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MRCP

Part I & II

Royal College of Physicians

4th Edition

The Only Notes You Will Ever Need

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PREFACE

These notes intended to target those who are appearing in MRCP exam. The idea behind it was collecting the most commonly tested topics and facts in the exam for my personal revision. The data has been collected from many sources.

This book was not prepared to be the primary studying source but it can help you after finishing your primary reading by arranging the thoughts in your mind and making every topic as short as possible by highlighting the most important points about it. You may use it just before going through your favorite MCQs book or internet site.

A friend of mine appeared in part one for couple of times, he reached to a conclusion and gave me a valuable advice that said 'when preparing for MRCP, study MRCP! Don't study medicine!' this book helps you to study MRCP rather than studying medicine. But at the end, you have to be a good physician otherwise MRCP will be a less valuable recognition, this is why I would advise to study medicine before you study MRCP and for sure before you say that you are a member of the Royal College you have to be upto the expectations.

This edition contains the latest guidelines including 2011 guidelines and recommendations. It is more organized than ever.

In the 4th edition we have added topics that matters for part two, we have added many pictures, we claim that it's just enough to get you through the second part comfortably.

The study pattern we recommend is:

1. Study one chapter of your choice from this book
2. Solve the same chapter's questions either on www.passmedicine.com, www.onexamination.com or www.pastest.co.uk
3. Study another chapter and go online to solve its question, continue until you finish all the chapters in the book and questions on your website of choice.
4. Revise the whole book.
5. Start solving questions randomly from another website (other than the website you have chosen to solve chapter by chapter)
6. Now you have probably solved at least 4000 BOF questions, you have seen all the question patterns in MRCP, now you need to stabilize the information you have gained through your journey
7. The **most important** step is to revise this book again just before the exam, this should be the last thing you do just before going to the exam. Solving question till the last moment is not recommended, you have probably gathered enough amount of information in your study, try to fix the information by reading this book.

All candidates who followed this pattern have passed comfortably and no single one gave us a negative feedback in both parts.

Hani Abuelgasim M., MD
Author

DEDICATION

To Mehiara, my late daughter who stole my heart and left
To my lovely Ahlam, who kept being patient and kind while I was studying
To my parents who always supported me
Hani Abuelgasim M.

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ALL BOXES WITH THIS COLOR ARE FOR MRCP PART II WRITTEN EXAM

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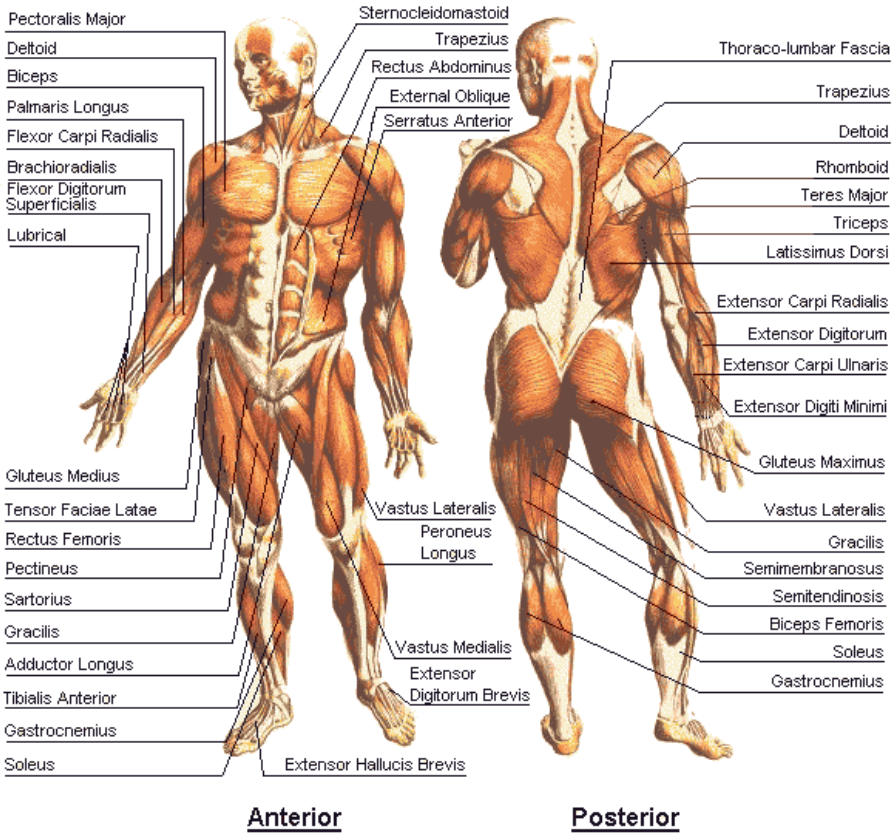
BASIC SCIENCES



HLAs: are encoded for by genes on chromosome 6. HLA A, B and C are class I antigens whilst DP, DQ, DR are class II antigens. Questions are often based around which diseases have strong HLA associations. The most important associations are listed below

HLA and autoimmune diseases	
HLA-B27	Ankylosing spondylitis
	Postgonococcal arthritis
	Acute anterior uveitis
	Reiter's syndrome (reactive arthritis)
HLA-DR2	Narcolepsy
	Goodpasture's
HLA-DR3	Autoimmune hepatitis
	Primary biliary cirrhosis
	Diabetes mellitus type 1
	Dermatitis herpetiformis
	Coeliac disease (95% associated with HLA-DQ2)
	Primary Sjögren syndrome
HLA-DR4	Rheumatoid arthritis
	Diabetes mellitus type 1 (> DR3)
HLA-DR3 + DR4 combined	Diabetes mellitus type 1
HLA-B47	21-hydroxylase deficiency
HLA-A3	Hemochromatosis
HLA-B5	Behcet's disease HLA B51 is a split of B5

Around 70% of patients with rheumatoid arthritis are HLA-DR4. Patients with Felty's syndrome (a triad of rheumatoid arthritis, splenomegaly and neutropaenia) are even more strongly associated with 90% being HLA-DR4

Clusters of Differentiation (CD): The table below lists the major clusters of differentiation (CD) molecules

CD1	HLA molecule that presents lipid molecules
CD2	Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion
CD3	The signalling component of the T cell receptor (TCR) complex
CD4	Co-receptor for HLA class II; also a receptor used by HIV to enter T cells
CD8	Co-receptor for HLA class I; also found on a subset of myeloid dendritic cells

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Hypersensitivity

The Gell and Coombs classification divides hypersensitivity reactions into 4 types

Type I - Anaphylactic

- Antigen reacts with IgE bound to mast cells
- Anaphylaxis, atopy

Type II - Cell bound

- Ig**G** or IgM binds to antigen on cell surface
- Autoimmune hemolytic anemia, ITP, **G**oodpasture's

Type III - Immune complex

- Free antigen and antibody (IgG, IgA) combine
- Serum sickness, SLE, post-streptococcal glomerulonephritis, extrinsic allergic alveolitis (especially acute phase)

Type IV - Delayed hypersensitivity

- T cell mediated
- Tuberculosis, Tuberculin skin reaction, grafT versus hosT disease, allergic conTacT dermaTiTis, scabies, exTrinsic allergic alveoliTis (especially chronic phase)

In recent times a further category has been added:

Type V - Stimulated hypersensitivity

- IgG antibodies stimulate cells they are directed against
- Graves', myasthenia Gravis

Allergy Tests

Skin prick test	Most commonly used test as easy to perform and inexpensive. Drops of diluted allergen are placed on the skin after which the skin is pierced using a needle. A large number of allergens can be tested in one session. Normally includes a **histamine (positive)** and sterile **water (negative)** control. A wheal will typically develop if a patient has an allergy. Can be interpreted after **15 minutes** Useful for **food** allergies and also **pollen** and **wasp/bee** venom
Radioallergosorbent test (RAST)	Determines the amount of IgE that reacts specifically with suspected or known allergens, for example IgE to egg protein. Results are given in grades from 0 (negative) to 6 (strongly positive) Useful for food allergies inhaled allergens (e.g. pollen) and wasp/bee venom Blood tests may be used when skin prick tests are not suitable, for example if there is extensive eczema or if the patient is taking antihistamines.
Skin patch testing	Useful **for contact dermatitis**. Around 30-40 allergens are placed on the back. Irritants may also be tested for. The results are read 48 hours later by a dermatologist

Immunoglobulins

IgG	75%	Monomer	Enhance pha**G**ocytosis of bacteria and viruses.
IgA	15%	Mono+Dimer	Found in secretions, provide localized protection on mucous membranes
IgM	10%	Pentamer	**first to be secreted, anti-A, B blood antibodies → Blood Transfusion**
IgD	1%	Monomer	Involved in activation of B cells
IgE	0.1%	Monomer	Involved in allergic reactions

Each day an average adult produces approximately 3gm of antibodies, about two-thirds of this IgA

1. **IgG**

- IgG makes up approximately 75% of the serum antibodies.
- IgG has a half-life of 7-23 days depending on the subclass.
- IgG is a monomer and has 2 epitope-binding sites
- The Fc portion of IgG can **activate the classical complement pathway.**
- The Fc portion of IgG can **bind to macrophage and neutrophils** for enhanced pha**G**ocytosis.
- The Fc portion of IgG can **bind to NK cells** for antibody-dependent cytotoxicity (ADCC).
- The Fc portion of IgG enables it to **cross the placenta**. (IgG is the only class of antibody that can cross the placenta and enter the fetal circulation).

2. **IgA**

- IgA makes up approximately 15% of the serum antibodies, it has a half-life of ≈ 5 days.
- IgA is found **mainly in body secretions** (saliva, mucous, tears, colostrum and milk) as **secretory IgA (sIgA)** where it **protects internal body surfaces exposed to the environment by blocking the attachment of bacteria and viruses to mucous membranes**.
- Secretory IgA is the most immunoglobulin produced.
- IgA is made primarily in the mucosal-associated lymphoid tissues (MALT).
- IgA appears as a dimer of 2 "Y"-shaped molecules and has 4 epitope-binding sites and a secretory component to protect it from digestive enzymes in the secretions
- The **Fc portion of secretory IgA binds to components of mucous** and contributes to the ability of mucous to trap microbes.
- IgA can activate the **alternative** complement pathway. (Ig**A** ≈ **A**lternate)

3. **IgM**

- IgM makes up approximately 10% of the serum antibodies and is **the first antibody produced during an immune response**.
- IgM has a half-life of about 5 days.
- IgM is a pentamer and has 10 epitope-binding sites
- The Fc portions of IgM are able to **activate the classical complement pathway** (most efficient)
- Monomeric forms of IgM are found on the surface of B-lymphocytes as **B-cell receptors** or **sIg**.

4. **IgD**

- IgD makes up approximately 1% of the serum antibodies.
- IgD is a monomer and has 2 epitope-binding sites.
- IgD is found on the surface of B-lymphocytes (along with monomeric IgM) as a **B-cell receptor** or **sIg** where it may control of B-lymphocyte activation and suppression.
- IgD may **play a role in eliminating B-lymphocytes generating self-reactive autoantibodies**.

5. **IgE**

- IgE makes up about 0.002% of the serum antibodies with a half-life of 2 days.
- Most IgE is tightly bound to basophils and mast cells via its Fc region.
- IgE is a monomer and has 2 epitope-binding sites.
- IgE is made in response to parasitic worms (helminths) and arthropods. It is also often made in response to allergens.
- IgE may protect external mucosal surfaces by **promoting inflammation**, enabling IgG, complement proteins, and leucocytes to enter the tissues.
- The Fc portion of IgE can **bind to mast cells and basophils** where it mediates many **allergic reactions**. Cross linking of cell-bound IgE by antigen triggers the release of vasodilators for an inflammatory response.
- The Fc portion of IgE **made against parasitic worms and arthropods can bind to eosinophils enabling opsonization**. This is a major defense against parasitic worms and arthropods.

Primary Immunodeficiency

Primary Immunodeficiency disorders may be classified according to which component of the immune system they affect

Neutrophil disorders

- Chronic granulomatous disease
- Chediak-higashi syndrome
- Leukocyte adhesion deficiency

B-cell disorders

- Ig**A** deficiency
- **B**ruton's congenital agammaglobulinemia
- **C**ommon variable immunodeficiency

T-cell disorders = DiGeorge

- DiGeorge syndrome is an example of a microdeletion syndrome. Patients are consequently at ↑ risk of viral and fungal infections.

Combined B- and T-cell disorders

- Severe combined immunodeficiency
- Ataxic telangiectasia (Autosomal recessive - 10% risk of developing malignancy, lymphoma or leukaemia, but also non-lymphoid tumours - recurrent chest infections)
- **Wiskott-Aldrich syndrome inherited in an X-linked recessive fashion and is thought to be caused by mutation in the WASP gene. Features include recurrent bacterial infections (e.g. chest), eczema and thrombocytopenia with low IgG.**

ANCA

There are two main types of anti-neutrophil cytoplasmic antibodies (ANCA) - cytoplasmic (cANCA) and perinuclear (pANCA)

For the exam, remember:

- cANCA - Wegener's Granulomatosis
- pANCA - Churg-Strauss syndrome + others (see below)

cANCA

- Most common target serine proteinase 3 (PR3)
- Some correlation between cANCA levels and disease activity
- Wegener's granulomatosis, positive in > 90%
- Microscopic polyangiitis, positive in 40%

pANCA

- Most common target is myeloperoxidase (MPO)
- **Cannot use level of pANCA to monitor disease activity**
- Associated with immune crescentic glomerulonephritis (positive in c. 80% of patients)
- Microscopic polyangiitis, positive in 50-75%
- Churg-Strauss syndrome, positive in 60%
- Wegener's granulomatosis, positive in 25%

Other causes of positive ANCA (usually pANCA)

- Inflammatory bowel disease (UC > Crohn's)
- Connective tissue disorders: RA, SLE, Sjogren's
- Autoimmune hepatitis

Whilst C3 deficiency is associated with recurrent bacterial infections, C5 deficiency is more characteristically associated with disseminated meningococcal infection

Complement Deficiencies

Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body. Complement proteins are involved in chemotaxis, cell lysis and opsonisation

C1 inhibitor (C1-INH) protein deficiency

- Causes hereditary angiedema
- C1-INH is a multifunctional serine protease inhibitor
- Probable mechanism is uncontrolled release of bradykinin resulting in edema of tissues

C1q, C1rs, C2, C4 deficiency (classical pathway components)

- Predisposes to immune complex disease
- E.g. SLE, Henoch-Schonlein Purpura

C3 deficiency

- Causes recurrent bacterial infections

C5 deficiency

- Predisposes to Leiner disease
- Recurrent diarrhea, wasting and seborrhoeic dermatitis
- Disseminated meningococcal infection.

C5-9 deficiency

- Encodes the membrane attack complex (MAC)
- Particularly prone to *Neisseria meningitidis* infection

Electrolytes and Its Imbalance

Metabolic Acidosis is commonly classified according to the anion gap. This can be calculated by: $(Na^+ + K^+) - (Cl^- + HCO^-_3)$. **If a question supplies the chloride level then this is often a clue that the anion gap should be calculated**. The normal range = 10-18 mmol/L

Normal anion gap (hyperchloraemic metabolic acidosis)

- Gastrointestinal bicarbonate loss: diarrhea, ureterosigmoidostomy, fistula
- Renal tubular acidosis
- Drugs: e.g. Acetazolamide
- Ammonium chloride injection
- Addison's disease

Renal tubular acidosis (RTA) causes a normal anion gap

Raised anion gap

- Lactate: shock, hypoxia
- Ketones: DKA, alcohol
- Urate: renal failure
- Acid poisoning: salicylates, methanol

Metabolic acidosis secondary to high lactate levels may be subdivided into two types:

- Lactic acidosis type A: shock, hypoxia, burns
- Lactic acidosis type B: metformin

Metabolic Alkalosis may be caused by a loss of hydrogen ions or a gain of bicarbonate. It is due mainly to problems of the kidney or gastrointestinal tract

Causes

- Vomiting / aspiration (e.g. Peptic ulcer leading to pyloric stenosis, nasogastric suction)
- Diuretics
- Liquorice, carbenoxolone
- Hypokalemia
- Primary hyperaldosteronism
- Congenital adrenal hyperplasia
- Cushing's syndrome
- Bartter's syndrome

Mechanism of metabolic alkalosis

- Activation of renin-angiotensin II-aldosterone (RAA) system is a key factor
- Aldosterone causes reabsorption of Na^+ in exchange for H+ in the distal convoluted tubule
- ECF depletion (vomiting, diuretics) → Na^+ and Cl^- loss → activation of RAA system → raised aldosterone levels
- In Hypokalemia, K^+ shift from cells → ECF. Alkalosis is caused by shift of H^+ into cells to maintain neutrality

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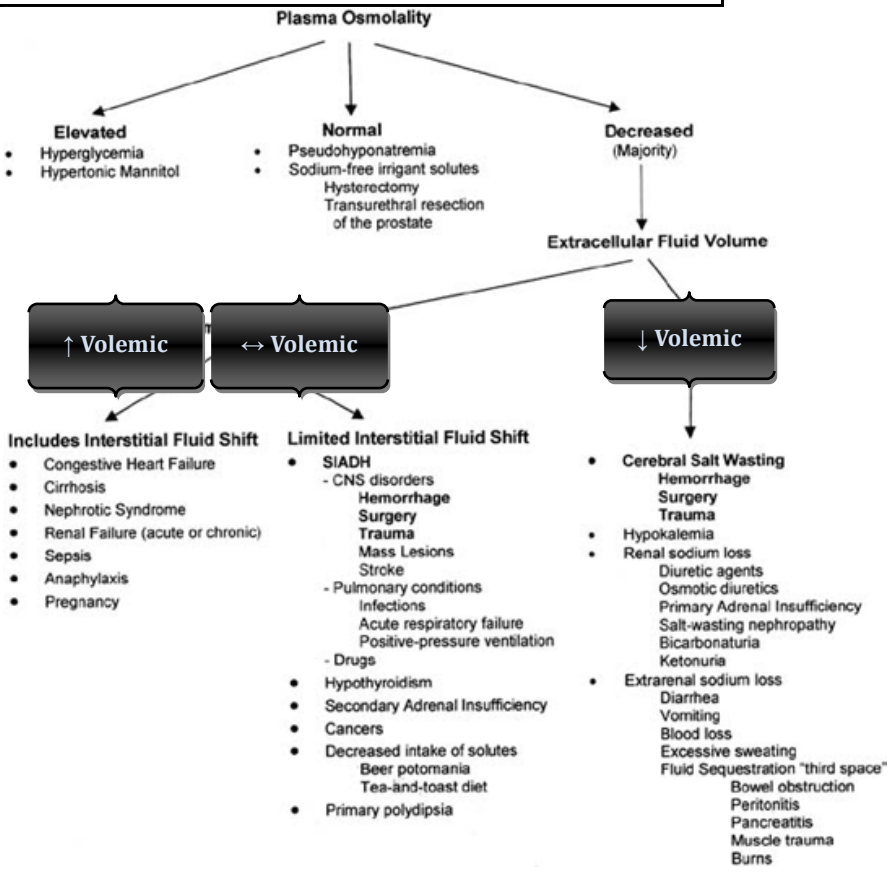
Hyponatremia may be caused by water excess or sodium depletion. **Causes of pseudohyponatremia include hyperlipidemia (↑ in serum volume) or a taking blood from a drip arm**. Urinary sodium and osmolarity levels aid making a diagnosis. It is important to note that every 100mg/dL increase of blood glucose will lower the Na as much as 1.6 meq.

	Hypertonic	Isotonic	Hypotonic
Plasma Osmolality	> 290	290-275	< 275



Urinary sodium > 20 mmol/L	Urinary sodium < 20 mmol/L
Sodium depletion, renal loss (patient often hypovolaemic) • Diuretics • Diuretic stage of renal failure • Addison's Patient often euvolaemic • SIADH (urine osmolality > 500 mmol/kg) • Hypothyroidism	Sodium depletion, extra-renal loss • Diarrhea, vomiting, sweating • Burns, adenoma of rectum Water excess (patient often hypervolaemic and edematous) • **Secondary** hyperaldosteronism: CCF, cirrhosis • ↓ GFR: renal failure with volume overload • IV dextrose, psychogenic polydipsia

Hypernatremia: Causes

- Dehydration
- Osmotic diuresis e.g. Hyperosmolar non-ketotic diabetic coma
- Diabetes insipidus
- Excess IV saline

Hyperkalemia:

Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels. Metabolic acidosis is associated with Hyperkalemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule. ECG changes seen in Hyperkalemia include Tall-Tented T Waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole

Causes of Hyperkalemia:

- Acute renal failure
- Drugs*: potassium sparing diuretics, ACE inhibitors, Cyclosporin
- Metabolic acidosis
- Addison's
- Rhabdomyolysis
- Massive blood transfusion

*β-blockers interfere with potassium transport into cells and can potentially cause Hyperkalemia in renal failure patients - remember β-agonists, e.g. salbutamol, are sometimes used as emergency treatment for hyperkalemia.

Untreated hyperkalaemia may cause life-threatening arrhythmias. Precipitating factors should be addressed (e.g. acute renal failure) and aggravating drugs stopped (e.g. ACE inhibitors). Management may be categorised by the aims of treatment

Stabilisation of the cardiac membrane

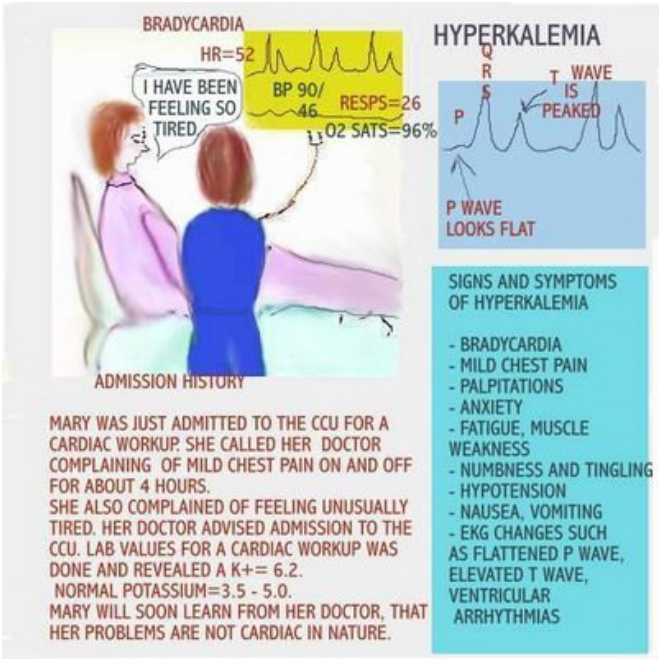
- intravenous calcium gluconate

Short-term shift in potassium from extracellular to intracellular fluid compartment

- combined insulin/dextrose infusion
- nebulised salbutamol

Removal of potassium from the body

- calcium resonium (orally or enema)
- loop diuretics
- dialysis



Hypokalemia

Potassium and hydrogen can be thought of as competitors. Hyperkalemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

Hypokalemia with alkalosis

- Vomiting
- Diuretics
- Cushing's syndrome
- Conn's syndrome (**primary** hyperaldosteronism)

Hypokalemia with acidosis:

- Diarrhea
- Renal tubular acidosis
- Acetazolamide
- Partially treated DKA

ECG features of hypokalemia:

- U waves
- Small or absent T waves (occasionally inversion)
- Prolong PR interval
- ST depression
- Long QT

In Hypokalemia, U have no Pot and no T, but a long PR and a long QT!

Hypomagnesemia:

Cause of low magnesium

- Diuretics
- Total Parenteral Nutrition (TPN)
- Diarrhea
- Alcohol
- Hypokalemia, hypocalcemia

Features

- Paraesthesia
- Tetany
- Seizures
- Arrhythmias
- ↓ PTH secretion → hypocalcemia
- ECG features similar to those of Hypokalemia
- Exacerbates digoxin toxicity

Hypophosphatemia

Causes

- Alcohol excess
- Acute liver failure
- Diabetic ketoacidosis
- Refeeding syndrome (like in anorexia nervosa management)
- Primary hyperparathyroidism
- Osteomalacia

Consequences

- Red blood cell hemolysis
- White blood cell and platelet dysfunction
- Muscle weakness and rhabdomyolysis
- Central nervous system dysfunction

Calcium Metabolism

Vitamin D ↑ plasma calcium and plasma phosphate levels by promoting renal tubular absorption and gut absorption of calcium and increasing renal phosphate reabsorption

The two hormones which primarily control calcium metabolism are:

- parathyroid hormone (PTH)
- vitamin D

Other hormones include

- Calcitonin: secreted from the C cells of the thyroid gland
- Thyroxine
- Growth hormone

Actions of parathyroid hormone (↑ plasma Ca from bones and kidneys and activation of Vit-D)

- ↑ plasma calcium, **↓ plasma phosphate**
- ↑ renal tubular reabsorption of calcium
- ↑ osteoclastic activity
- ↑ renal conversion of 25-hydroxy vitamin D to 1,25 dihydroxy vitamin D
- **↓ renal phosphate reabsorption**

Actions of vitamin D (↑ plasma Ca from bones and kidneys and GIT)

- ↑ plasma calcium and **↑ plasma phosphate**
- ↑ renal tubular reabsorption and gut absorption of calcium
- ↑ osteoclastic activity
- **↑ renal phosphate reabsorption**

FYI	Corrected Ca^{+} = measures Ca^{+} $_{(mmol/l)}$ + [40 - S.Albumin $_{(g/dl)}$] x 0.027

Hypocalcemia

The clinical history combined with **parathyroid hormone levels will reveal the cause of hypocalcemia** in the majority of cases

Causes

- Vitamin D deficiency (osteomalacia)
- Chronic renal failure
- Hypoparathyroidism (e.g. Post thyroid/parathyroid surgery)
- Pseudohypoparathyroidism (target cells insensitive to PTH)
- Rhabdomyolysis (initial stages)
- Magnesium deficiency (due to end organ PTH resistance)

Acute pancreatitis may also cause hypocalcemia. Contamination of blood samples with EDTA may also give falsely low calcium levels

Hypocalcemia causes Prolonged QT in ECG

Osteomalacia causes hypocalcemia associated with a low serum phosphate

Cisplatin, often used in the management of non-small cell lung cancer, is a well known cause of magnesium deficiency. Without first correcting magnesium levels it is difficult to reverse hypocalcemia

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcemia seen a result of neuromuscular excitability

Features

- Tetany: muscle twitching and spasm
- Perioral paraesthesia
- If chronic: depression, cataracts
- ECG: prolonged QT interval

Hypocalcemia: Trousseau's sign is more sensitive and specific than Chvostek's sign

Trousseau's sign

- Carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- Wrist flexion and fingers drawn together
- Seen in around 95% of patients with hypocalcemia and around 1% of normocalcaemic people

Chvostek's sign

- Tapping over parotid causes facial muscles to twitch
- Seen in around 70% of patients with hypocalcemia and around 10% of normocalcaemic people

Management

- Acute management of severe hypocalcemia is with intravenous replacement. The preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
- Intravenous calcium chloride is more likely to cause local irritation
- ECG monitoring is recommended
- Further management depends on the underlying cause

Hypercalcemia

The most common causes of hypercalcemia are malignancy (bone metastases, myeloma, PTHrP from squamous cell lung cancer) and primary hyperparathyroidism

One of the key differentiating features between monoclonal gammopathy of uncertain significance (MGUS) and myeloma is the absence of complications such as immune paresis, hypercalcemia and bone pain

Other causes include

- Sarcoidosis*
- Vitamin D intoxication
- Acromegaly
- Thyrotoxicosis
- Milk-alkali syndrome
- Drugs: thiazides, Ca^{++} containing antacids
- Dehydration
- Addison's disease
- Paget's disease of the bone**

Parathyroid hormone levels are useful, as malignancy and primary hyperparathyroidism are the two most common causes of hypercalcemia. A parathyroid hormone that is normal or raised suggests primary hyperparathyroidism.

Hypercalemia causes short QT in ECG

*other causes of granulomas may lead to hypercalcemia e.g. tuberculosis and histoplasmosis
**usually normal in this condition but hypercalcemia may occur with prolonged immobilization

Management

The initial management of hypercalcemia is rehydration with normal saline, typically 3-4 litres/day. Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days

Other options include:

- Calcitonin - quicker effect than bisphosphonates
- Steroids in sarcoidosis

There is a limited role for the use of furosemide in hypercalcemia. It may be useful in patients who cannot tolerate aggressive fluid rehydration

Hyperuricemia ↑ levels of uric acid may be seen secondary to either ↑ cell turnover or ↓ renal excretion of uric acid. Hyperuricemia may be found in asymptomatic patients who have not experienced attacks of gout

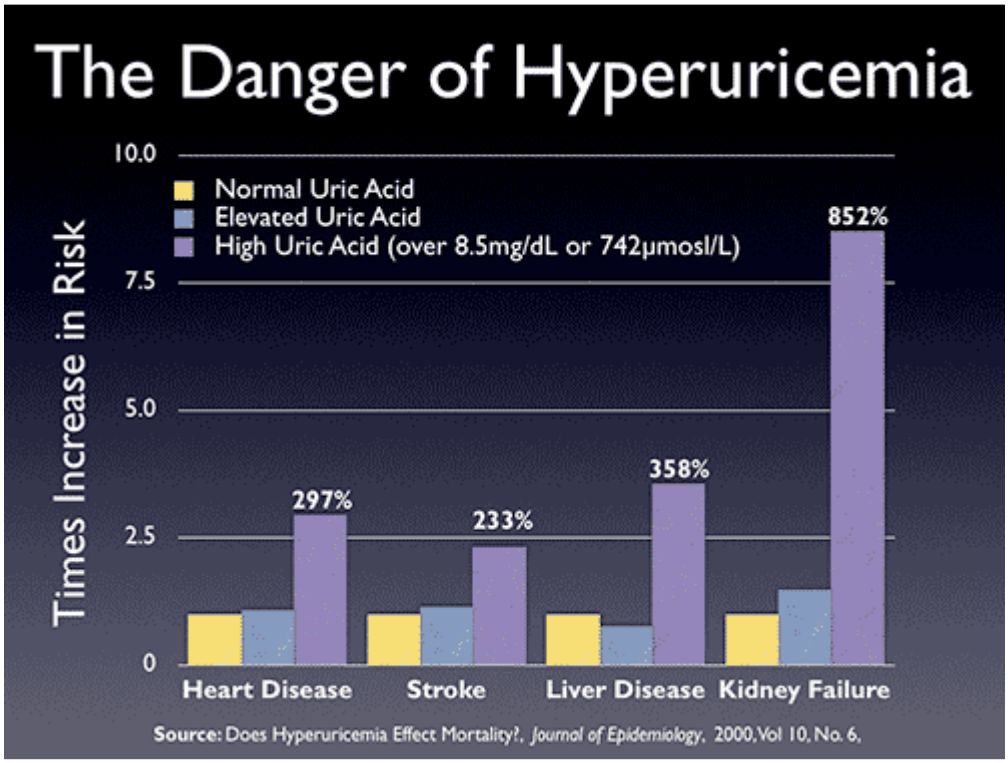
Hyperuricemia may be associated with both hyperlipidemia and hypertension. It may also be seen in conjunction with the metabolic syndrome

↑ Synthesis:

- Lesch-Nyhan disease
- Myeloproliferative disorders
- Diet rich in purines
- Exercise
- Psoriasis
- Cytotoxics

↓ Excretion:

- Drugs: low-dose aspirin, diuretics, pyrazinamide
- Pre-eclampsia
- Alcohol
- Renal failure
- Lead



Body & Diseases Markers

Acute Phase Proteins:

The following proteins ↑:

- CRP
- ferritin
- fibrinogen
- α-1 antitrypsin
- caeruloplasmin
- serum amyloid A
- serum amyloid P component
- haptoglobin
- complement

During the acute phase response the liver ↓ the production of other proteins (sometimes referred to as negative acute phase proteins).

The following proteins ↓:

- albumin
- transthyretin (formerly known as prealbumin)
- transferrin
- retinol binding protein
- cortisol binding protein

Rheumatoid factor is an IgM antibody against IgG

Rheumatoid Factor (RF) is a circulatinjg antibody (usually IgM) which reacts with antigenic sites on the Fc portion of the patients own IgG

RF can be detected by:

- Rose-Waaler test: sheep red cell agglutination
- Latex agglutination test (less specific)

RF is positive in 70-80% of patients with rheumatoid arthritis; **high titre levels are associated with severe progressive disease (prognosis but NOT a marker of disease activity)**

Other conditions associated with a positive RF include:

- Sjogren's syndrome (around 100%)
- Felty's syndrome (around 100%)
- Infective endocarditis (= 50%)
- SLE (= 20-30%)
- Systemic sclerosis (= 30%)
- General population (= 5%)
- Rarely: TB, HBV, EBV, leprosy

Nitric Oxide: vasodilation+inhibits platelet aggregation

Nitric Oxide previously known as endothelium derived relaxation factor, nitric oxide (NO) has emerged as a molecule which is integral to many physiological and pathological processes. It is formed from **L-arginine** and oxygen by nitric oxide synthetase (NOS). An inducible form of NOS has been shown to be present in macrophages. Nitric oxide has a very short half-life (seconds), being inactivated by oxygen free radicals

Effects

- Acts on guanylate cyclase leading to raised intracellular cGMP levels and therefore decreasing Ca^{++} levels
- Vasodilation, mainly venodilation
- Inhibits platelet aggregation

Clinical relevance

- Underproduction of NO is implicated in hypertrophic pyloric stenosis
- Lack of NO is thought to promote atherosclerosis
- **In sepsis ↑ levels of NO contribute to septic shock**
- Organic nitrates (metabolism produces NO) is widely used to treat cardiovascular disease (e.g. Angina, heart failure)
- Sildenafil is thought to potentiate the action of NO on penile smooth muscle and is used in the treatment of erectile dysfunctions

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Atrial Natriuretic Peptide (ANP) is a powerful vasodilator, and a protein (polypeptide) **hormone** secreted by heart muscle cells. It is involved in the homeostatic control of body water, sodium, potassium and fat (adipose tissue). ANP acts to ↓ the water, sodium and adipose loads on the circulatory system, thereby **reducing blood pressure**

Basics

- Secreted mainly from myocytes of **right atrium** and ventricle in response to ↑ blood volume
- Secreted by both the right and left atria (right >> left)
- 28 amino acid peptide hormone, which acts via cGMP
- Degraded by endopeptidases

Actions

- Natriuretic, i.e. Promotes excretion of sodium
- Lowers BP
- **Antagonises** actions of angiotensin II, aldosterone

BNP - actions:

- **Vasodilator**
- **Diuretic and natriuretic**
- **Suppresses both sympathetic tone and the renin-angiotensin-aldosterone system**

B-type Natriuretic Peptide (BNP) **hormone** produced mainly by the **left ventricular** myocardium in response to strain

Whilst heart failure is the most obvious cause of raised BNP levels any cause of left ventricular dysfunction such as myocardial ischemia or valvular disease may raise levels. Raised levels may also be seen due to ↓ excretion in patients with chronic kidney disease. Factors which ↓ BNP levels include: treatment with ACE inhibitors, angiotensin-2 receptor blockers and diuretics.

Clinical uses of BNP

Diagnosing patients with acute dyspnea

- A low concentration of BNP(< 100pg/ml) makes a diagnosis of heart failure unlikely, but raised levels should prompt further investigation to confirm the diagnosis
- NICE currently recommends BNP as a helpful test to rule out a diagnosis of heart failure

Prognosis in patients with chronic heart failure

- Initial evidence suggests BNP is an extremely useful marker of prognosis

Guiding treatment in patients with chronic heart failure

- Effective treatment lowers BNP levels

Screening for cardiac dysfunction

- Not currently recommended for population screening

Endothelin is a potent, long-acting vasoconstrictor and bronchoconstrictor. It is secreted initially as a **prohormone** by the vascular endothelium and later converted to ET-1 by the action of endothelin converting enzyme. It acts via interaction with a G-protein linked to phospholipase C leading to calcium release. Endothelin is thought to be important in the pathogenesis of many diseases including primary pulmonary hypertension (endothelin antagonists are now used), cardiac failure, hepatorenal syndrome and Raynaud's

Promotes release

- Angiotensin II
- ADH
- Hypoxia
- Mechanical shearing forces

Inhibits release

- Nitric oxide
- Prostacyclin

Raised levels in

- MI
- Heart failure
- ARF
- Asthma
- Primary pulmonary hypertension

Tumour Necrosis Factor (TNF) is a **pro-inflammatory cytokine** with multiple roles in the immune system

TNF is secreted mainly by macrophages and has a number of effects on the immune system, acting mainly in a paracrine fashion:

- Activates macrophages and neutrophils
- Acts as costimulator for T cell activation
- **Key mediator of bodies response to gram NEGATIVE septicemia**
- Similar properties to IL-1
- Anti-tumour effect (e.g. Phospholipase activation)

TNF-α binds to p55 and p75 receptors, these receptors can induce apoptosis. It also cause activation of NFkB

Endothelial effects include ↑ expression of selectins and ↑ production of platelet activating factor, IL-1 and prostaglandins. TNF promotes the proliferation of fibroblasts and their production of protease and collagenase. It is thought fragments of receptors act as binding points in serum. Systemic effects include pyrexia, ↑ acute phase proteins and disordered metabolism leading to cachexia. TNF is important in the pathogenesis of rheumatoid arthritis - TNF blockers (e.g. infliximab, etanercept) are now licensed for treatment of severe rheumatoid.

TNF blockers

- Infliximab: monoclonal antibody, IV administration
- Etanercept: fusion protein that reversibly binds soluble TNF receptors, subcutaneous administration
- Adalimumab: monoclonal antibody, subcutaneous administration
- Adverse effects of TNF blockers include reactivation of latent tuberculosis and demyelination

Infliximab is also used in active Crohn's disease unresponsive to steroids

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Interferons (IFN) are **cytokines** released by the body in response to viral infections and neoplasia. They are classified according to cellular origin and the type of receptor they bind to. **IFN-α and IFN-β bind to type-1 receptors, whilst IFN-gamma binds only to type-2 receptors.**

IFN-α (aLpha)

- Produced by Leucocytes
- Antiviral action
- Useful in hepatitis B & C, kaposi's sarcoma, metastatic renal cell cancer, hairy cell leukemia
- Adverse effects include fLu-Like symptoms and depression

IFN-β

- Produced by fibro**B**lasts
- Antiviral action
- ↓ the frequency of exacerbations in patients with relapsing-remitting MS

IFN-gamma

- Produced by T lymphocytes & NK cells
- weaker antiviral action (inhibit viral duplication), more of a role in immunomodulation particularly macrophage activation
- May be useful in chronic granulomatous disease and osteopetrosis

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Leukotrienes are **fatty molecules** of the immune system that contribute to inflammation in asthma and bronchitis. Leukotriene antagonists are used to treat asthma and bronchitis.

Function

- Mediators of inflammation and allergic reactions
- Cause bronchoconstriction, mucous production
- ↑ vascular permeability, attract leukocytes
- Leukotriene D4 has been identified as the SRS-A (slow reacting substance of anaphylaxis)

Production

- secreted by leukocytes
- **formed from arachidonic acid by action of lipoxygenase**
- it is thought that the NSAID induced bronchospasm in asthmatics is secondary to the express production of leukotrienes due to the inhibition of prostaglandin synthetase

---

Interleukin 1 (IL-1) is a **key mediator of the immune response**. It is **secreted mainly by macrophages and monocytes** and acts as a costimulator of T cell and B cell proliferation. **While TNF is secreted mainly by macrophages, it is a key mediator of body response to gram NEGATIVE septicemia and it is a costimulator of T cell.**

Other effects include increasing the expression of adhesion molecules on the endothelium. By stimulating the release by the endothelium of vasoactive factors such as PAF, nitric oxide and prostacyclin it also causes vasodilation and ↑ vascular permeability. **It is therefore one of the mediators of shock in sepsis.** Along with IL-6 and TNF, it acts on the hypothalamus causing pyrexia.

T-Helper Cells: There are two major subsets of T-Helper cells:

Th1

- Involved in the cell mediated response and delayed (type IV) hypersensitivity
- Secrete IFN-gamma, IL-2, IL-3

Th2

- Involved in mediating humoral (antibody) immunity
- e.g. Stimulating production of IgE in asthma
- Secrete IL-4, IL-5, IL-6, IL-10, IL-13

Cardiac and Protien Markers: Interpretation of the various cardiac enzymes has now largely been superceded by the introduction of troponin T and I. Questions still however commonly appear in the MRCP

The components of thin filaments are troponin, tropomyosin and actin. Thick filaments are primarily composed of myosin

Key points for the exam

- Myoglobin is the first to rise
- CK-MB is useful to look for reinfarction as it returns to normal after 2-3 days (troponin T remains elevated for up to 10 days)

	Begins to rise	Peak value	Returns to normal
Myoglobin	1-2 hours	6-8 hours	1-2 days
CK-MB	2-6 hours	16-20 hours	2-3 days
CK	4-8 hours	16-24 hours	3-4 days
Trop T	4-6 hours	12-24 hours	7-10 days
AST	12-24 hours	36-48 hours	3-4 days
LDH	24-48 hours	72 hours	8-10 days

Alkaline Phosphatase (ALP)

Causes of raised alkaline phosphatase (ALP)

- Liver: cholestasis, hepatitis, fatty liver, neoplasia
- Paget's
- Osteomalacia
- Bone metastases
- Hyperparathyroidism
- Renal failure
- Physiological: pregnancy, growing children, healing fractures

The table below splits the causes according to the calcium level

Raised ALP and raised calcium	Raised ALP and low calcium
• Paget's • Bone metastases • Hyperparathyroidism	• Osteomalacia • Renal failure

ESR is a non-specific marker of inflammation and depends on both the size, shape and number of red blood cells and the concentration of plasma proteins such as fibrinogen, α2-globulins and gamma globulins

Causes of a high ESR

- Temporal arteritis
- Myeloma
- Other connective tissue disorders e.g. Systemic lupus erythematosus
- Other malignancies
- Infection
- Other factors which raise ESR: increasing age, ♀ sex, anemia

Causes of a low ESR

- Polycythemia
- Afibrinogenemia/hypofibrinogenemia

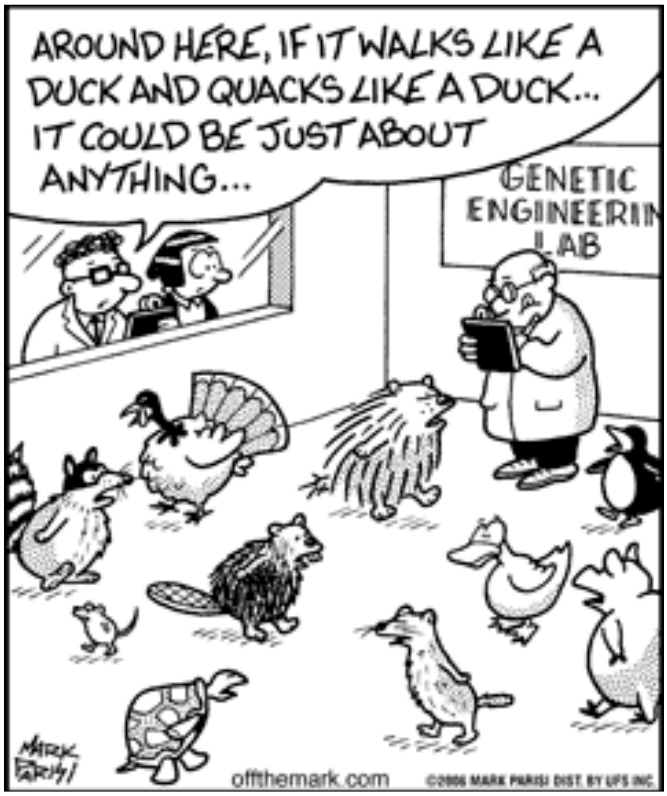
Leukocyte alkaline phosphatase:

Raised in

- Myelofibrosis
- Leukemoid reactions
- Polycythemia rubra vera
- Infections
- Steroids, Cushing's syndrome
- Pregnancy, oral contraceptive pill

Low in

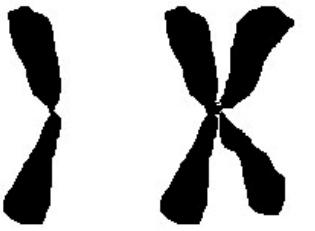
- Chronic myeloid leukemia
- Pernicious anemia
- Paroxysmal nocturnal hemoglobinuria
- Infectious mononucleosis



Genetic & Heridetary Disorders

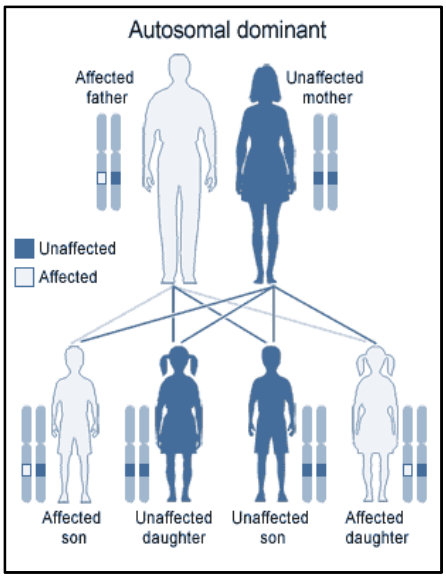
Definitions:

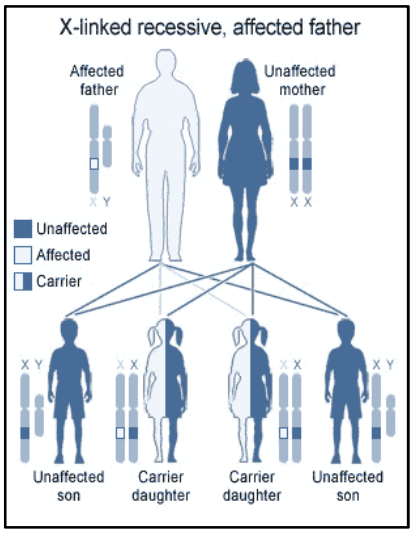
- Gene: a region of DNA that encodes protein
- Genome: complete set of gene of an organism and the intervening DNA sequence
- Locus: site of gene on a chromosome
- Chromosome: Self-replicating genetic structure of cells containing the cellular DNA that bears in its nucleotide sequence the linear array of genes. Chromosomes are normally found in pairs; human beings typically have 23 pairs of chromosomes (22 autosome + 1 sex chromosome)
- Alleles: Alternative form of a gene found at the same locus on a chromosome; a single allele for each locus is inherited separately from each parent.

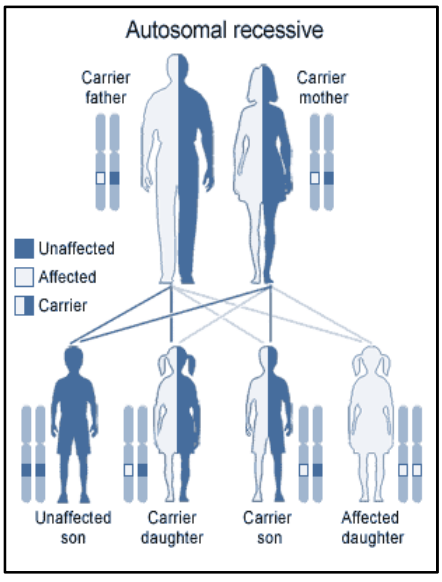


haploid chromosome diploid chromosome

- Haploid: a single set of chromosomes (half the full set of genetic material), present in the gamete (egg or sperm) = (23).
- Codon: sequence of amino acid
- Karyotype: number and appearance of chromosomes in the nucleus, in human there are 44 autosome + 2 sex chromosomes
- Autosome: any chromosome other than sex chromosome (22 pairs)







Autosomal RECESSIVE conditions are 'METABOLIC' - exceptions: inherited ataxias
Autosomal DOMINANT conditions are 'STRUCTURAL' - exception: hyperlipidemia type II, hypokalaemic periodic paralysis

Autosomal Recessive Conditions

NB autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

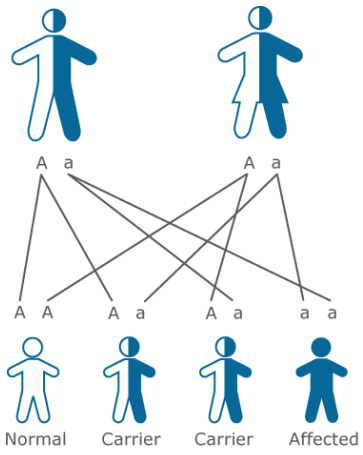
- Mucopolysaccharidoses: Hunter's (X-linked recessive)
- G6PD (X-linked recessive)

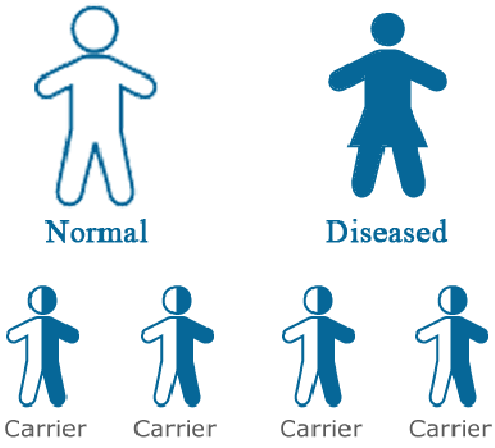
In autosomal recessive inheritance

- Only homozygotes are affected
- ♂s and ♀s are equally likely to be affected
- Does not manifest in every generation - may 'skip a generation'

If two heterozygote parents (Carrier Parents)

- 25% chance of having an affected (homozygote) child
- 50% chance of having a carrier (heterozygote) child
- 25% chance of having an unaffected (i.e. Genotypical) child





If one affected parent (i.e. homozygote for gene) and one unaffected (i.e. not a carrier or affected)

- All the children will be carriers

Autosomal recessive disorders are often metabolic in nature and are generally more life-threatening compared to autosomal dominant condition

Both parents are cariers → each offspring has risk of 25% being affected and 50% being carier
Results from mutation of 2 copies (alleles) of the autosomal gene

The following conditions are **autosomal recessive**: (most of Cs andGs are recessive)

- Albinism
- Ataxia telangiectasia
- Congenital adrenal hyperplasia
- Cystic fibrosis
- Cystinuria
- Familial Mediterranean Fever
- Fanconi anemia
- Friedreich's ataxia
- Galactosemia
- Gaucher
- Gilbert's syndrome (this is still a matter of debate and many textbooks will list Gilbert's as AD)
- Glycogen storage disease
- Gunther disease (congenital erythropoietic porphyria CEP)
- Hemochromatosis
- Homocystinuria
- Limb-girdle muscular dystrophy
- Lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick
- Maple Syrup Urine Diease
- Mucopolysaccharidoses like Hurler's (all of them except Hunter's)
- Niemann-Pick
- Oculocutaneous Albinism
- Phenylketonuria PKU
- Sickle cell
- Tay-Sach's
- Thalassemias
- Wilson's disease

- some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidemia type II and hypokalaemic periodic paralysis are autosomal dominant
- some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive

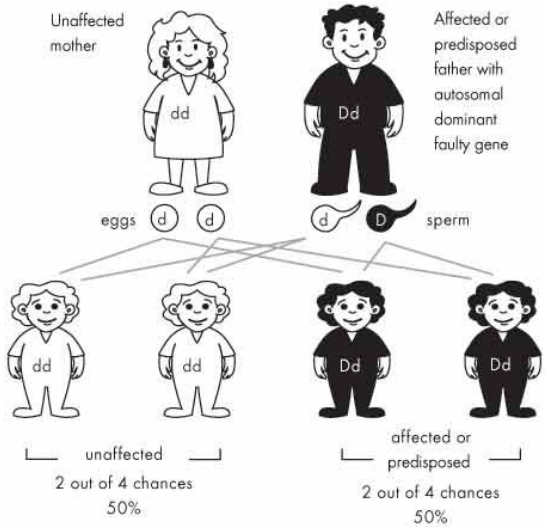
A= Albinism.
B= beta thalessemia.
C= Cystic Fibrosis.
D= Deafness.
E= Emphysema (alpha-1 Antitrypsin Deficiency).
F= Friedrichs ataxia.
G= Gauchers disease.
H= Homocystinuria, Hemochromatosis.

Autosomal Dominant Conditions:

AD conditions: all offsprings of an affected person have 50% chance of inherting the mutation
Results from mutation of 1 copy (allele) of the autosomal gene

The following conditions are **autosomal dominant:** (most of Hs, MNs and Vs are dominant)

- Achondroplasia
- Acute intermittent porphyria (all hepatic porphyrias except congenital erythropoietic porphyria)
- Adult polycystic disease
- Antithrombin III deficiency
- Ehlers-Danlos syndrome
- Familial adenomatous polyposis (including Gardner syndrome)
- Familial hypercholesterolemia
- Hereditary hemorrhagic telangiectasia
- Hereditary motor and sensory neuropathy (HMSN) including Charcot–Marie–Tooth
- Hereditary spherocytosis
- Hereditary non-polyposis colorectal carcinoma
- Huntington's disease
- Hyperlipidemia type II
- Hypokalaemic periodic paralysis
- Malignant hyperthermia
- Marfan's syndromes
- Myopathies (most of them including HOCM, Ocular Myopathy)
- Myotonic dystrophy
- Neurofibromatosis
- Noonan syndrome
- Osteogenesis imperfecta
- Peutz-Jeghers syndrome
- Retinoblastoma
- Romano-Ward syndrome
- Tuberose sclerosis
- Von Hippel-Lindau syndrome
- Von Willebrand's disease*



*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

In autosomal dominant diseases:

- Both homozygotes and heterozygotes manifest disease (**THERE IS NO CARRIER STATE**)
- Both ♂s and ♀s affected
- Only affected individuals can pass on disease
- Disease is passed on to 50% of children
- Normally appears in every generation (although see below)
- Risk remains same for each successive pregnancy

Complicating factors:

- Non-penetrance: lack of clinical signs and symptoms (normal phenotype) despite abnormal gene. e.g. 40% otosclerosis
- Spontaneous mutation: new mutation in one of gametes e.g. 80% of individuals with achondroplasia have unaffected parents

Hemophilia is an X-linked recessive disorder and would hence be expected only to occur in ♂s. As patients with Turner's syndrome only have one X chromosome however, they may develop X-linked recessive conditions

X-linked Recessive inheritance: only ♂s are affected. An exception to this seen in examinations is patients with Turner's syndrome, who are affected due to only having one X chromosome. X-linked recessive disorders are transmitted by heterozygote ♀s (carriers) and ♂-to-♂ transmission is not seen. Affected ♂s can only have unaffected sons and carrier daughters.

X-linked recessive conditions - no ♂-to-♂ transmission

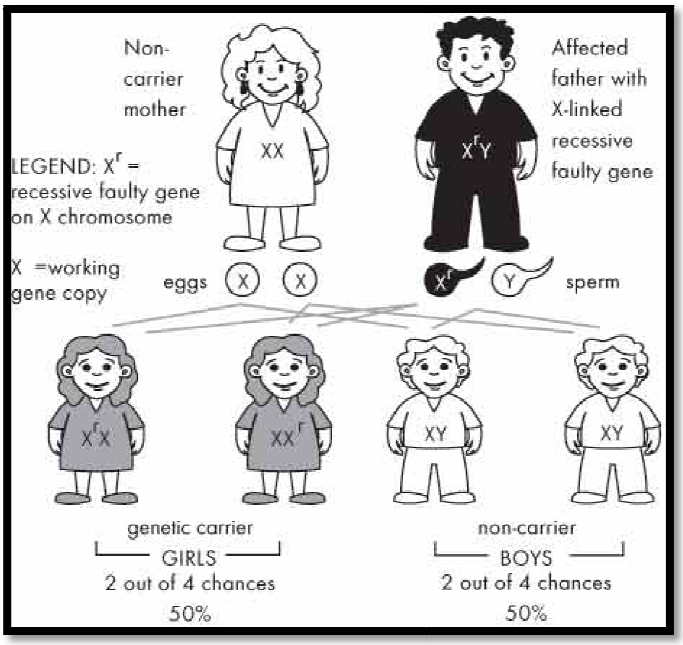
Each ♂ child of a heterozygous ♀ carrier has a 50% chance of being affected whilst each ♀ child of a heterozygous ♀ carrier has a 50% chance of being a carrier

The possibility of an affected father having children with a heterozygous ♀ carrier is generally speaking extremely rare. However, in certain Afro-Caribbean communities G6PD deficiency is relatively common and homozygous ♀s with clinical manifestations of the enzyme defect are seen.

Sons of carier ♀ have 50% chance of being affected while daughters have 50% chance of being cariers.
Daughters of affected ♂ are carriers (100%).
Father is affected and mother is carrier then all kids have 50% chance of being affected.

The following conditions are inherited in an X-linked recessive fashion:

- Androgen insensitivity syndrome
- Becker muscular dystrophy
- Color blindness
- Duchenne muscular dystrophy
- Fabry's disease
- G6PD deficiency
- Hemophilia A,B
- Hunter's disease
- Kallman Syndrome (X-Linked Trait)
- Lesch-Nyhan syndrome
- Nephrogenic diabetes insipidus
- Ocular albinism
- Retinitis pigmentosa
- Severe combined immunodeficiency
- **Wiskott-Aldrich syndrome combined B+T primary immunodeficiency and is thought to be caused by mutation in the WASP gene. Features include recurrent bacterial infections (e.g. chest), eczema and thrombocytopenia with low IgG.**



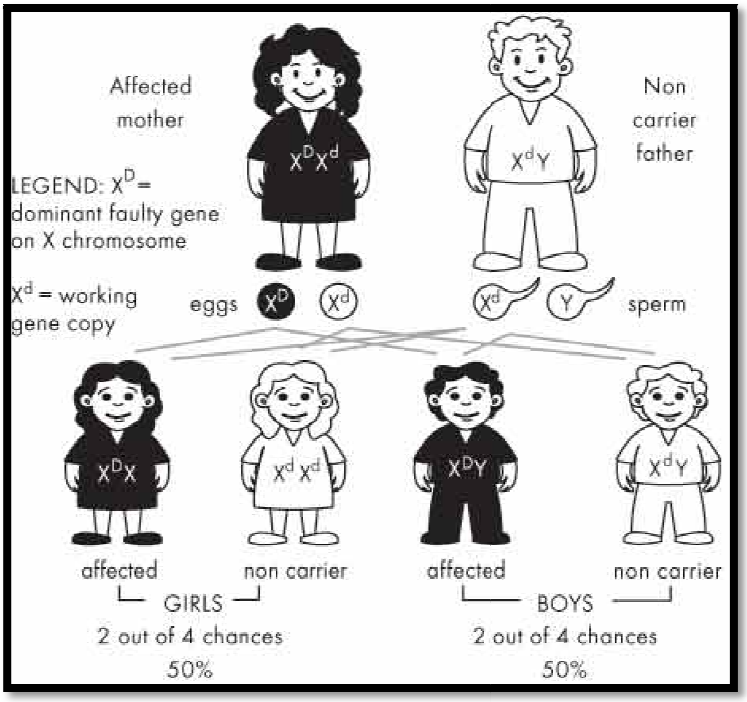
The following diseases have varying patterns of inheritance, with the majority being in an X-linked recessive fashion:

- Chronic granulomatous disease (in > 70%) – (Primary Immunodeficiency, Neutrophil disorder)

X-linked Dominant: ♀s have two X chromosomes, while ♂s have one X and one Y chromosome. If a child has inherited the mutation from the X chromosome of one of their parents they will have the condition. A woman with an X-linked dominant disorder has a 50% chance of having an affected daughter or son with each pregnancy. The sons of a man with an X-linked dominant disorder will not be affected (since they inherit their only X chromosome from their mother), but his daughters will all inherit the condition.

XLD:

- Vit D resistant Rickets
- Alport syndrome (85% XLD)
- Rett syndrome



(Anticipation) in trinucleotide repeat disorders = **earlier onset** in successive generations

The 'classic' definition of anticipation is earlier onset in successive generations. However, in most cases, an ↑ in the severity of symptoms is also noted.

Trinucleotide Repeat Disorders are genetic conditions caused by an abnormal number of repeats (expansions) of a repetitive sequence of three nucleotides. These expansions are unstable and may enlarge which may lead to an earlier age of onset in successive generations - a phenomenon known as anticipation*. In most cases, an ↑ in the severity of symptoms is also noted

Examples - note dominance of neurological disorders

- Fragile X (CGG)
- Huntington's (CAG)
- Myotonic dystrophy (CTG)
- Friedreich's ataxia* (GAA)
- Spinocerebellar ataxia
- Spinobulbar muscular atrophy
- Bulbospinal Neuropathy
- Dentatorubral pallidoluysian atrophy

*Friedreich's ataxia is unusual in not demonstrating anticipation

Mitochondrial Diseases: Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA

Mitochondrial inheritance have the following characteristics:

- Inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote
- **All** children of affected ♂s will not inherit the disease
- **All** children of affected ♀s will inherit it
- Generally encode rare neurological diseases
- Poor genotype:phenotype correlation
- Heteroplasmy: within a tissue or cell there can be different mitochondrial populations

Histology

- Muscle biopsy classically shows **'red, ragged fibres'** due to ↑ number of mitochondria

Examples include:

- Leber's optic atrophy
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- MERRF syndrome: myoclonus epilepsy with ragged-red fibres
- Pearson syndrome: characterized by sideroblastic anemia and exocrine pancreas dysfunction. It is usually fatal in infancy. The few patients who survive into adulthood often develop symptoms of Kearns-Sayre syndrome.
- Kearns-Sayre syndrome: onset in patients < 20 years old, external ophthalmoplegia, retinitis pigmentosa. Ptosis may be seen
- Sensorineural hearing loss
- Neuropathy, ataxia, and retinitis pigmentosa (NARP)

Tumour Suppressor Genes

Basics

- Genes which normally control the cell cycle
- Exhibit a recessive effect - both copies must be mutated before cancer occurs

Examples

- P53
- APC: colorectal cancer
- NF-1: neurofibromatosis
- RB: retinoblastoma

myc is an oncogene which encodes a transcription factor

P53 Gene is a tumour suppressor gene located on chromosome 17p. It is the most commonly mutated gene in breast, colon and lung cancer

P53 is thought to play a crucial role in the cell cycle, preventing entry into the S phase until DNA has been checked and repaired. It may also be a key regulator of apoptosis

Li-Fraumeni Syndrome is a rare autosomal dominant disorder characterized by the early onset of a variety of cancers such as sarcomas and breast cancer. It is caused by mutation in the p53 gene.

Down Syndrome: trisomy 21 or G, is a chromosomal disorder caused by the presence of all or part of an extra 21st chromosome. The condition is characterized by a combination of major and minor differences in structure. Often Down syndrome is associated with some impairment of cognitive ability and physical growth, and a particular set of facial characteristics. Down syndrome in a fetus can be identified with amniocentesis during pregnancy or in a baby at birth.

Clinical features

- Face: upslanting palpebral fissures, epicanthic folds, Brushfield spots in iris, protruding tongue, small ears, round/flat face
- Flat occiput
- Single palmar crease, pronounced 'sandal gap' between big and first toe
- Hypotonia
- Congenital heart defects (40-50%, see below)
- Duodenal atresia
- Hirschsprung's disease
- **♀: subfertility**
- **♂: infertility**

Cardiac complications

- Multiple cardiac problems may be present
- **Endocardial cushion defect (40%, also known as atrioventricular septal canal defects)**
- Ventricular septal defect (30%)
- Secundum atrial septal defect (10%)
- Tetralogy of fallot (5%)
- Isolated patent ductus arteriosus (5%)

Later complications

- Subfertility: ♂s are almost always infertile due to impaired spermatogenesis. ♀s are usually subfertile, and have an ↑ incidence of problems with pregnancy and labour
- Learning difficulties
- Short stature
- Repeated respiratory infections (+hearing impairment from glue ear)
- **Acute lymphoblastic leukemia**
- Hypothyroidism
- Alzheimer's
- Atlantoaxial instability

Risk of Down's syndrome with increasing maternal age

- Risk at 30 years = 1/1000
- 35 years = 1/350
- 40 years = 1/100
- 45 years = 1/30

One way of remembering this is by starting at 1/1,000 at 30 years and then dividing by 3 (i.e. 3 times more common) for every extra 5 years of age

Cytogenetics

Mode	% of cases	Risk of recurrence
Non-dysjunction	94%	1 in 100 if mother < 35 years
Robertsonian translocation (usually onto 14)	5%	10-15% if mother is translocation carrier 2.5% if father is translocation carrier
Mosaicism	1%	

The chance of a further child with Down's syndrome is approximately 1 in 100 if the mother is less than 35 years old. If the trisomy 21 is a result of a translocation the risk is much higher

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Turner Syndrome is a chromosomal disorder affecting around 1 in 2,500 ♀s. It is caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes. Turner's syndrome is denoted as 45, XO or 45 X

There is ↑ incidence of autoimmune disease (especially autoimmune thyroiditis) and Crohn's disease

Features

- Short stature
- Shield chest, widely spaced nipples
- Webbed neck
- **Bicuspid aortic valve (15%), coarctation of the aorta (5-10%)**
- Primary amenorrhoea
- High-arched palate
- Short fourth metacarpal
- Multiple pigmented naevi
- Lymphedema in neonates (especially feet)

Klinefelter Syndrome (Hypogonadotropic hypogonadism) is associated with karyotype 47, XXY

Features

- Often taller than average
- Lack of secondary sexual characteristics
- Small, firm testes (hypogonadism)
- Infertile
- Gynaecomastia - ↑ incidence of breast cancer
- **Elevated gonadotrophin levels**

Diagnosis is by chromosomal analysis
↓
Karyotyping

Klinefelter's - LH & FSH raised
Kallman's - LH & FSH low-normal

If the LH and FSH levels are inappropriately low-normal with a low testosterone concentration, that points towards a diagnosis of hypogonadotrophic hypogonadism.

Kallman Syndrome is a recognised cause of delayed puberty secondary to hypogonadotrophic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallman's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus. The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty.

Features

- 'Delayed puberty'
- Hypogonadism, cryptorchidism (including undescended tests)
- Anosmia
- Sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- Patients are typically of normal or above average height
- Cleft lip/palate and visual/hearing defects are also seen in some patients

---

Marfan Syndrome is an autosomal dominant connective tissue disorder. It is caused by a defect in the fibrillin-1 gene on chromosome 15

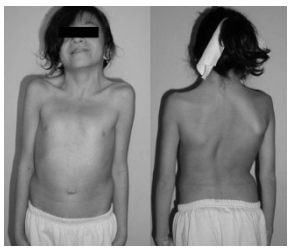
Features

- Tall stature with arm span > height ratio > 1.05
- High-arched palate
- Arachnodactyly (***spider fingers;*** fingers are abnormally long, in some cases all or few fingers can be bent backwards of 180 degrees)
- Pectus excavatum
- Pes planus
- Scoliosis of > 20 degrees
- **Heart: dilation of the aortic sinuses (seen in 90%) which may lead to aortic regurgitation, mitral valve prolapse (75%), aortic dissection**
- Lungs: repeated pneumothoraces
- Eyes: upwards lens dislocation (superotemporal ectopia lentis), blue sclera

---

Noonan Syndrome: Often thought of as the '♂ Turner's', Noonan's syndrome is an autosomal dominant condition associated with a normal karyotype. It is thought to be caused by a defect in a gene on chromosome 12. As well as features similar to Turner's syndrome (webbed neck, widely-spaced nipples, short stature, pectus carinatum and excavatum), a number of characteristic clinical signs may also be seen:

- Cardiac: pulmonary valve stenosis
- Ptosis
- Triangular-shaped face
- Low-set ears
- Coagulation problems: factor XI deficiency



Fragile X is a trinucleotide repeat disorder, complex X-linked inheritance.

Features in ♂s

- Learning difficulties
- **Large** low set ears, **Long** thin face, **High** arched palate
- Macroorchidism (**Large** testes)
- Hypotonia
- Autism is more common
- **Mitral valve prolapse**

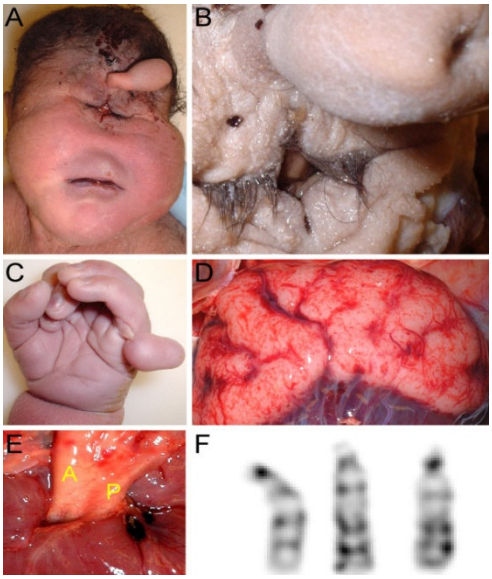
Features in ♀s (who have one fragile chromosome and one normal X chromosome) range from normal to mild

Diagnosis

- Can be made antenatally by chorionic villus sampling or amniocentesis
- Analysis of the number of CGG repeats using restriction endonuclease digestion and southern blot analysis

---

Patau Syndrome, also known as trisomy 13 and trisomy D, is a chromosomal abnormality, a syndrome in which a patient has an additional chromosome 13 due to a non-disjunction of chromosomes during meiosis. Some are caused by Robertsonian translocations. The extra chromosome 13 disrupts the normal course of development, causing the characteristic features of Patau syndrome. Like all non-disjunction conditions (Down syndrome, Edwards syndrome, etc.), the risk of this syndrome in the offspring ↑ with maternal age at pregnancy, with about 31 years being the average. Patau syndrome affects approximately 1 in 25,000 live births.



♂ **infant with Patau, demonstrating alobar holoprosencephaly with cyclopia**. **A)** Facial features included sloping forehead with a proboscis superior to a single central palpebral fissure. **B)** Close-up of the fused eyelids and proboscis showing a single nostril. **C)** Polydactyly showing six digits. **D)** Posterior view of the brain showing indistinct gyri, fusion of the hemispheres, and occipital encephalocele.**E)** Transposition of the aorta (A), and hypoplastic pulmonary trunk (P). **F)** Trisomy 13 [47, XY, +13] (karyotype by Giemsa-banding)

Of those embryos that do survive to gestation and subsequent birth, common abnormalites include:

- Mental & motor challenge
- Polydactyly (extra digits)
- Microcephaly
- Low-set ears
- Holoprosencephaly (failure of the forebrain to divide properly).
- Heart defects
- Structural eye defects, including microphthalmia, peters anomaly, cataract, iris and/or fundus (coloboma), retinal dysplasia or retinal detachment, sensory nystagmus, cortical visual loss, and optic nerve hypoplasia
- Cleft palate
- Meningomyelocele (a spinal defect)
- Omphalocele (abdominal defect)
- Abnormal genitalia
- Abnormal palm pattern

- Overlapping of fingers over thumb.
- Cutis aplasia (missing portion of the skin/hair)
- Prominent heel
- Kidney defects
- Deformed feet known as "rocker-bottom feet"

Prader-Willi Syndrome is an example of genetic imprinting where the phenotype depends on whether the deletion occurs on a gene inherited from the mother or father:

- Prader-Willi syndrome if gene deleted from father
- Angelman syndrome if gene deleted from mother

Prader-Willi syndrome is associated with the absence of the active Prader-Willi gene on the long arm of chromosome 15 (same as Marfan's chromosome). This may be due to:

- Microdeletion of paternal 15q11-13 (70% of cases)
- Maternal uniparental disomy of **chromosome 15**

Features

- Hypotonia during infancy
- Dysmorphic features
- Short stature
- Hypogonadism and infertility
- Learning difficulties
- Childhood obesity
- Behavioural problems in adolescence
- Acanthosis nigricans

Edwards Syndrome Trisomy 18 (also known as Trisomy E or Edwards Syndrome) is a genetic disorder caused by the presence of all or part of an extra 18th chromosome. **It is the second most common autosomal trisomy, after Down's Syndrome**, that carries to term.

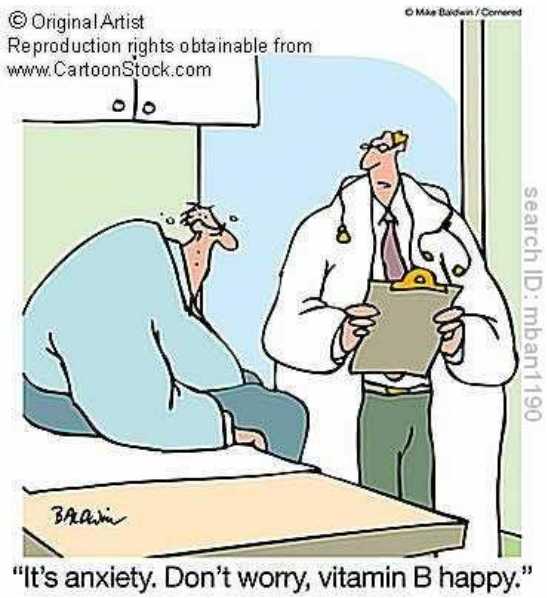
Trisomy 18 is caused by the presence of three—as opposed to two—copies of chromosome 18 in a fetus or infant's cells. The incidence of the syndrome is estimated as 1 in 3,000 live births. Incidence ↑ as the mother's age ↑. The syndrome has a very low rate of survival, resulting from heart abnormalities, kidney malformations, and other internal organ disorders.

Infants born with Edward's syndrome may have some or all of the following characteristics:

- Kidney malformations
- Structural heart defects at birth
- Intestines protruding outside the body (omphalocele)
- Esophageal atresia
- Mental retardation
- Developmental delays
- Growth deficiency
- Feeding difficulties
- Breathing difficulties
- Arthrogryposis (a muscle disorder that causes multiple joint contractures at birth)
- Microcephaly accompanied by a prominent occiput

- Low-set, malformed ears
- Abnormally small jaw (micrognathia)
- Cleft lip/cleft palate
- Upturned nose
- Narrow eyelid folds (palpebral fissures)
- Widely-spaced eyes (ocular hypertelorism)
- Ptosis
- A short sternum
- Clenched hands
- Underdeveloped thumbs and or nails
- Absent radius
- Webbing of the second and third toes
- Clubfoot or ***rocker bottom feet***,
- Undescended testicles

Trisomy 13	Patau Syndrome	Trisomy D
Trisomy 18	Edward Syndrome	Trisomy E
Trisomy 21	Down Syndrome	Trisomy G



Vitamins Deficincies

Vitamin	Chemical name	Deficiency state
A	Retinoids	Night-blindness (nyctalopia)
B1	Thiamine	Beriberi • Polyneuropathy, Wernicke-Korsakoff syndrome • Heart failure
B3	Niacin (Nicotinic Acid)	Pellagra • Dermatitis • Diarrhea • Dementia
B6	Pyridoxine	Anemia, irritability, seizures
B7	Biotin	Dermatitis, seborrhoea
B9	Folic acid	Megaloblastic anemia, deficiency during pregnancy - neural tube defects
B12	Cyanocobalamin	Megaloblastic anemia
C	Ascorbic acid	Scurvy • Gingivitis • Bleeding
D	Ergocalciferol, cholecalciferol	Rickets, osteomalacia (good source is cod liver oil)
E	Tocopherol, tocotrienol	Mild hemolytic anemia in newborn infants, ataxia, peripheral neuropathy
K	Naphthoquinone	Hemorrhagic disease of the newborn, bleeding diathesis

Pellagra is a caused by nicotinic acid (niacin) Vitamin B3 deficiency. The classical features are the 3 D's - dermatitis, diarrhea and dementia

Pellagra may occur as a consequence of isoniazid therapy (isoniazid inhibits the conversion of tryptophan to niacin)

Features

- Dermatitis (brown scaly rash on sun-exposed sites - termed Casal's necklace if around neck)
- Diarrhea
- Dementia, depression
- Death if not treated

Vitamin B12 is actively absorbed in the Terminal Ileum

Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system. It is absorbed after binding to intrinsic factor (secreted from parietal cells in the stomach) and is actively absorbed in the terminal ileum. A small amount of vitamin B12 is passively absorbed without being bound to intrinsic factor.

Causes of vitamin B12 deficiency

- Pernicious anemia
- Post gastrectomy
- Poor diet
- Disorders of terminal ileum (site of absorption): crohn's, blind-loop etc
- Metformin

Features of vitamin B12 deficiency

- Macrocytic anemia
- Sore tongue and mouth
- Neurological symptoms: e.g. Ataxia
- Neuropsychiatric symptoms: e.g. Mood disturbances

Management

- If no neurological involvement 1 mg of IM hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months
- If a patient is also deficient in folic acid then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration of the cord

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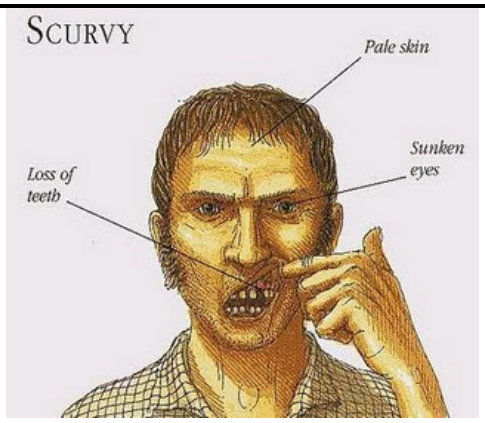
Vitamin C Deficiency (scurvy) leads to defective synthesis of collagen resulting in capillary fragility (bleeding tendency) and poor wound healing



Features

- Gingivitis, loose teeth
- Poor wound healing
- Bleeding from gums, hematuria, epistaxis
- General malaise

Vitamin D-Resistant Rickets is an **X-linked dominant** (along with Rett and Alport syndrome) condition which usually presents in infancy with failure to thrive. It is caused by impaired phosphate reabsorption in the renal tubules

Features

- Failure to thrive
- Normal serum calcium, low phosphate, elevated alkaline phosphotase
- X-ray changes: cupped metaphyses with widening of the epiphyses

Diagnosis is made by demonstrating ↑ urinary phosphate

Management

- High-dose vitamin D supplements
- Oral phosphate supplements

Folic acid is also present in liver, green vegetables and nuts

Folate Metabolism

Drugs which interfere with metabolism

- Trimethoprim
- Methotrexate
- Pyrimethamine

Drugs which can ↓ absorption

- Phenytoin

Iron Metabolism

Absorption

- Upper small intestine
- About 10% of dietary iron absorbed
- Fe^{++} (ferrous iron) much better absorbed than Fe^{+++} (ferric iron)
- Absorption is regulated according to bodies need
- ↑ by vitamin C, gastric acid
- ↓ by proton pump inhibitors, tetracycline, gastric achlorhydria, tannin (found in tea)

Distribution in body

- Total body iron = 4g
- Hemoglobin = 70%
- Ferritin and hemosiderin = 25%
- Myoglobin = 4%
- Plasma iron = 0.1%

Transport

- Carried in plasma as Fe^{+++} bound to transferrin

Storage

- Stored as ferritin in tissues

Excretion

- Lost via intestinal tract following desquamination

Zinc Deficiency:

Features

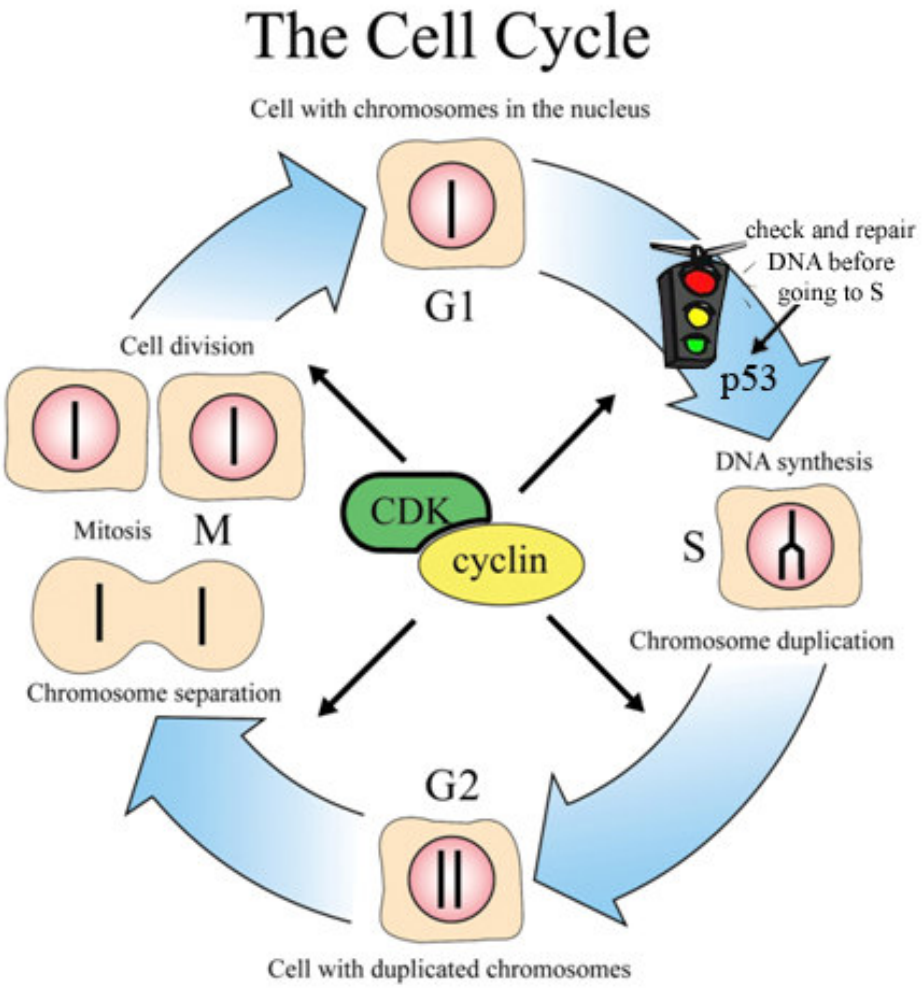
- Perioral dermatitis: red, crusted lesions
- Acrodermatitis
- Alopecia
- Short stature
- Hypogonadism
- Hepatosplenomegaly
- Geophagia (ingesting clay/soil)
- Cognitive impairment

Cellular and Molecular Anatomy

Cell Organelles

The table below summarises the main functions of the major cell organelles:

Organelle/macromolecule	Main function
Endoplasmic reticulum	Translation and folding of new proteins (rough endoplasmic reticulum), expression of lipids (smooth endoplasmic reticulum)
Golgi apparatus	Sorting and modification of proteins
Mitochondrion	Energy production. Contains mitochondrial genome as circular **double stranded DNA**
Nucleus	DNA maintenance and RNA transcription
Lysosome	Breakdown of large molecules such as proteins and polysaccharides
Nucleolus	Ribosome production
Ribosome	Translation of RNA into proteins
Peroxisome	Breakdown of metabolic hydrogen peroxide
Proteasome	Along with lysosome pathway: degradation of large protein molecules



M - Mitosis - cell division
G1 - Gap phase 1 - determines length of cell cycle - under influence of p53
S - DNA Synthesis
G2 - Gap phase

Membrane Receptors: There are four main types of membrane receptor:

Ligand-gated ion channel

- Generally mediate fast responses
- E.g. **nicotinic acetylcholine**, GABA-A & GABA-C, glutamate receptors

Tyrosine kinase receptors

- Contain intrinsic enzyme activity
- E.g. Insulin, growth factors, interferon

Guanylate cyclase receptors

- Contain intrinsic enzyme activity
- E.g. Atrial natriuretic factor (ANP), nitric oxide receptors

G protein-coupled receptors

- Generally mediate slow transmission and affect metabolic processes
- Activated by a wide variety of extracellular signals e.g. Peptide hormones, biogenic amines, lipophilic hormones and light.
- Consist of 3 main subunits: α, β and gamma
- Ligand binding → conformational changes to receptor, this induces exchange of GDP for GTP
- E.g. **Muscarinic acetylcholine**, adrenergic receptors, GABA-B

Adrenoceptors

α-1 (Agonist → phenylephrine)

- Vasoconstriction
- Relaxation of GI smooth muscle
- Salivary secretion
- Hepatic glycogenolysis

α-2 (Agonist → clonidine)

- Mainly presynaptic: inhibition of transmitter release (inc NA, Ach from autonomic nerves)
- Inhibits insulin
- Platelet aggregation

β-1 (Agonist → dobutamine)

- Mainly located in the heart
- ↑ heart rate + force

β-2 (Agonist → salbutamol)

- Vasodilation
- Bronchodilation
- Relaxation of GI smooth muscle

β-3 (Agonist → being developed, may have a role in preventing obesity)

- Lipolysis

Pathways

- All are G-protein coupled
- α-1:activate phospholipase C → IP3 → DAG
- α-2: inhibit adenylate cyclase
- β-1: stimulate adenylate cyclase
- β-2: stimulate adenylate cyclase
- β-3: stimulate adenylate cyclase

Second Messengers

Overview

- Many different types
- Allow amplification of external stimulus

Cyclic AMP

- E.g. Adrenaline, noradrenaline, glucagon, LH, FSH, TSH, calcitonin, parathyroid hormone

Protein kinase activity

- E.g. Insulin, growth hormone and factor, prolactin, oxytocin, erythropoietin.

Calcium and/or phosphoinositides

- E.g. ADH, GnRH, TRH

Cyclic GMP

- E.g. ANP, nitric oxide

Molecular Biology Techniques

Molecular biology techniques

- Snow (**S**outh - **NO**rth - **W**est)
- Drop (**D**NA - **R**NA - **P**rotein)

The following table shows a very basic summary of molecular biology techniques

Southern blotting	Detects DNA
Northern blotting	Detects RNA
Western blotting	Detects and quantifies proteins

Polymerase Chain Reaction (PCR) is a molecular genetic investigation technique. The main advantage of PCR is its sensitivity: **only one strand of sample DNA is needed to detect a particular DNA sequence**. It now has many uses including prenatal diagnosis, detection of mutated oncogenes and diagnosis of infections. PCR is also extensively used in forensics. **Prior to the procedure it is necessary to have two DNA oligonucleotide primers**. These are complimentary to specific DNA sequences at either end of the target DNA

Initial prep

- Sample of DNA is added to test tube along with two DNA primers
- A thermostable DNA polymerase (Taq) is added

The following cycle then takes place

- Mixture is heated to almost boiling point causing denaturing (uncoiling) of DNA
- Mixture is the allowed to cool: complimentary strands of DNA pair up, as there is an excess of the primer sequences they pair with DNA preferentially

The above cycle is then repeated, with the amount of DNA doubling each time

Reverse transcriptase PCR

- Used to amplify RNA
- **RNA is converted to DNA by reverse transcriptase**
- Gene expression in the form of mRNA (rather than the actually DNA sequence) can therefore be analyzed

---

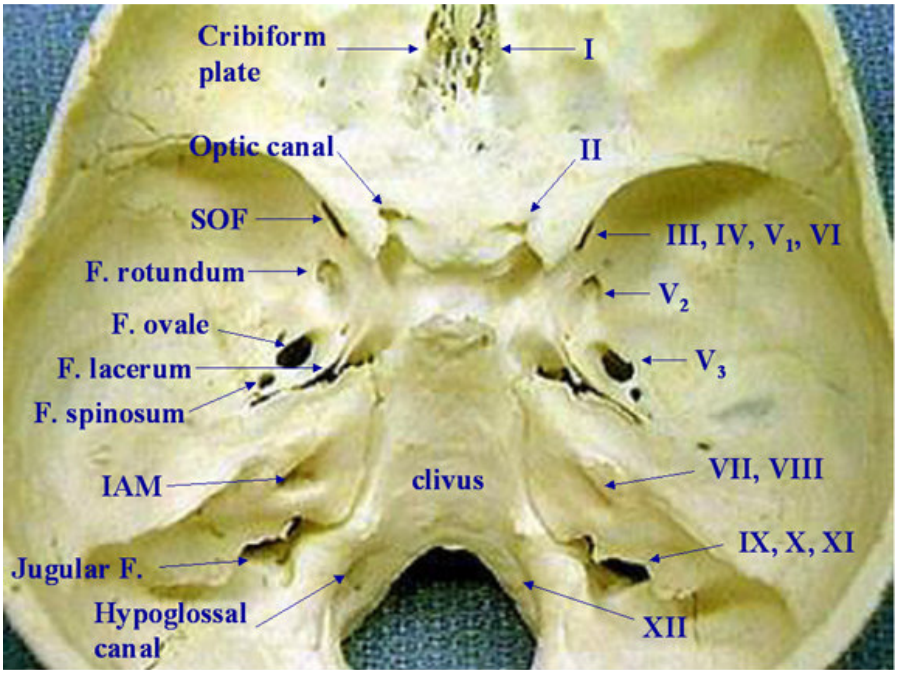
The human genome is stored on 23 chromosome pairs. The haploid human genome has a total of 3 billion DNA base pairs, making up estimated 20,000-25,000 protein-coding genes

Gross Anatomy

Foramina of the skull

Questions asking about foramina of the skull have come up in the exam in previous years.

Foramen	Bone	Vessels	Nerves
Optic canal	Sphenoid	Ophthalmic A.	Optic nerve (II)
Superior orbital fissure	Sphenoid	Superior ophthalmic V. Inferior ophthalmic V.	Oculomotor nerve (III) Trochlear nerve (IV) lacrimal, frontal and nasociliary branches of ophthalmic nerve (V_1) Abducent nerve (VI)
Inferior orbital fissure	Sphenoid and maxilla	Inferior ophthalmic V. Infraorbital artery Infraorbital vein	Zygomatic nerve and infraorbital nerve of maxillary nerve (V_2) Orbital branches of pterygopalatine ganglion
Foramen Rotundum	Sphenoid	-	Maxillary nerve (V_2)
Foramen Ovale	Sphenoid	Accessory meningeal A.	Mandibular nerve (V_3)
Jugular Foramen	Occipital and temporal	Posterior meningeal A. Ascending pharyngeal A. Inferior petrosal sinus Sigmoid sinus Internal jugular V.	Glossopharyngeal nerve (IX) Vagus nerve (X) Accessory nerve (XI)



Renal Anatomy: The tables below show the anatomical relations of the kidneys:

Right kidney

Direct contact	Layer of peritoneum in-between
Right suprarenal gland Duodenum Colon	Liver Distal part of small intestine

Left kidney

Direct contact	Layer of peritoneum in-between
Left suprarenal gland Pancreas Colon	Stomach Spleen Distal part of small intestine

Skin

Epidermis is the outermost layer of the skin and is composed of a stratified squamous epithelium with an underlying basal lamina

It may be divided in to five layers:

Layer	Description
Stratum **C**orneum	Flat, dead, scale-like cells filled with keratin - Continually shed
Stratum **L**ucidum	Clear layer - present in thick skin only
Stratum **G**ranulosum	Cells form links with neighbours
Stratum **S**pinosum	Squamous cells begin keratin synthesis Thickest layer of epidermis
Stratum **G**erminativum AKA: *startum basale*	The basement membrane - single layer of columnar epithelial cells **Gives rise to keratinocytes** **Contains melanocytes**

Physiology

Myocardial Action Potential

Phase	Description	Mechanism
0	Rapid depolarisation	Rapid sodium influx These channels automatically deactivate after a few ms
1	Early repolarisation	Efflux of potassium
2	Plateau	Slow influx of calcium
3	Final repolarisation	Efflux of potassium
4	Restoration of ionic concentrations	Resting potential is restored by Na^+/K^+ ATPase There is slow entry of Na^+ into the cell decreasing the potential difference until the threshold potential is reached, triggering a new action potential

NB cardiac muscle remains contracted 10-15 times longer than skeletal muscle

Conduction velocity

Atrial conduction	Spreads along ordinary atrial myocardial fibres at 1 m/sec
AV node conduction	0.05 m/sec
Ventricular conduction	Purkinje fibres are of large diameter and achieve velocities of 2-4 m/sec (this allows a rapid and coordinated contraction of the ventricles

---

Antidiuretic hormone (ADH) is secreted from the posterior pituitary gland. It promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels

The adrenal medulla secretes virtually all the adrenaline in the body as well as secreting small amounts of noradrenaline. It essentially represents an enlarged and specialised sympathetic ganglion

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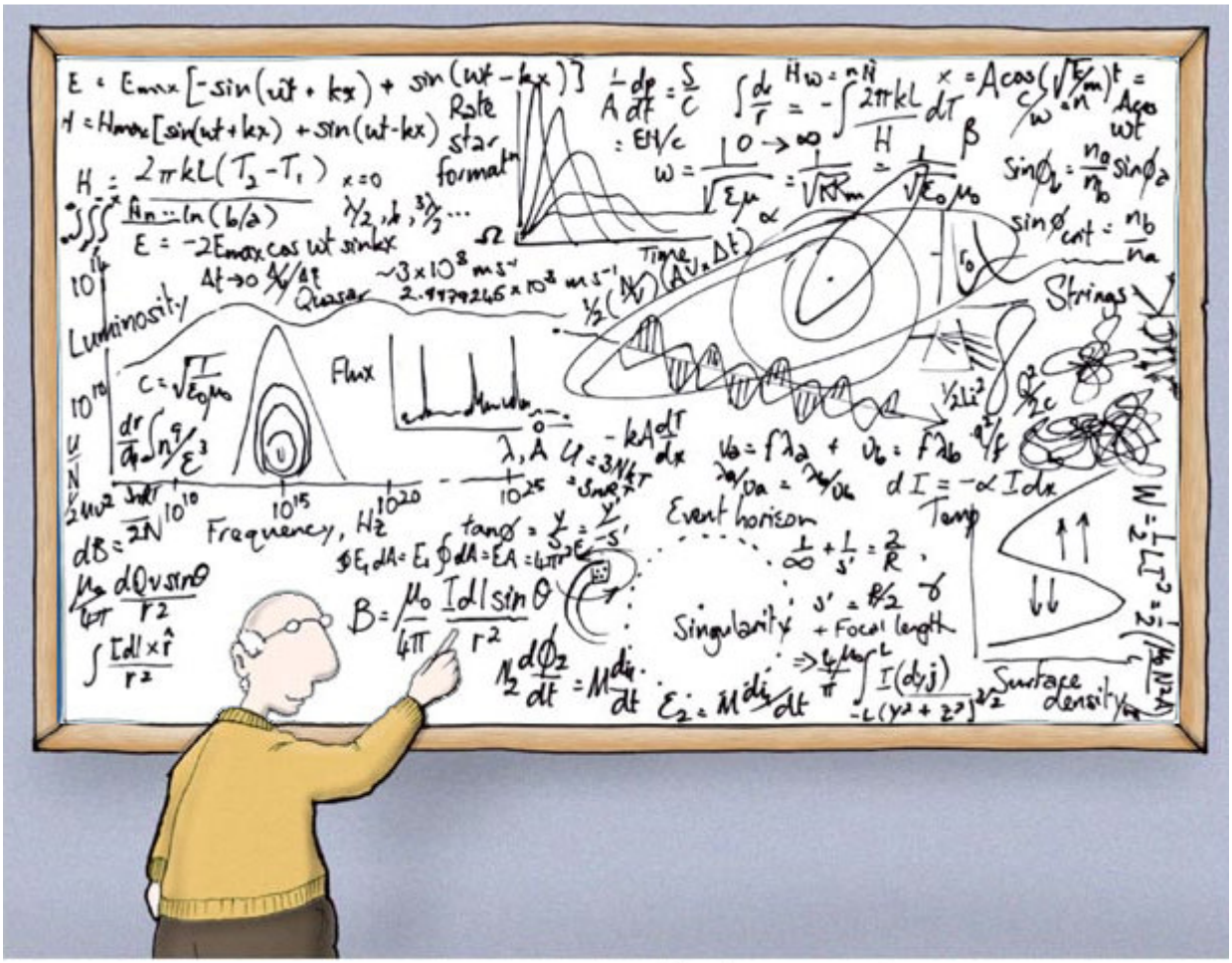
STATISTICS
&
EVIDENCE BASED MEDICINE



Statistics Made Simple

Significance Tests

A null hypothesis states that two treatments are equally effective (and is hence negatively phrased); A significance test uses the sample data to assess how likely the null hypothesis is to be correct. **The p value is the probability of obtaining a result at least as extreme as the one that was actually observed, assuming that the null hypothesis is true**.

The null hypothesis is rejected if the p-value is smaller than or equal to the significance level

P-value ≤ significance level

For example: There is no difference in the prevalence of colorectal cancer in patients taking low-dose aspirin compared to those who are not

The alternative hypothesis is the opposite of the null hypothesis, i.e. there is a difference between the two treatments.

Two types of errors may occur when testing the null hypothesis

- Type I: the null hypothesis is rejected when it is true - i.e. Showing a difference between two groups when it doesn't exist (= significance level)
- Type II: the null hypothesis is accepted when it is false - i.e. Failing to spot a difference when one really exists

The **power of a study** is the probability of (correctly) rejecting the null hypothesis when it is false

- power = 1 - the probability of a type II error
- power can be ↑ by increasing the sample size

Types:

The type of significance test used depends on whether the data is parametric (something which can be measured, or normally distributed) or non-parametric

Correlation

- Parametric (normally distributed): Pearson's coefficient
- Non-parametric: Spearman's coefficient

Parametric tests

- Student's t-test - paired or unpaired
- Pearson's product-moment coefficient - correlation

Non-parametric tests

- Mann-Whitney - unpaired data
- Wilcoxon matched-pairs - compares two sets of observations on a single sample
- Chi-squared test - used to compare proportions or percentages
- Spearman, Kendall rank – correlation
- McNemar's test is used on nominal data to determine whether the row and column marginal frequencies are equal

Paired data refers to data obtained from a single group of patients, e.g. Measurement before and after an intervention. Unpaired data comes from two different groups of patients, e.g. Comparing response to different interventions in two groups

Funnel plots - show publication bias in meta-analyses

Funnel Plot is primarily used to demonstrate the existence of publication bias in meta-analyses. Funnel plots are usually drawn with treatment effects on the horizontal axis and study size on the vertical axis.

Interpretation

- A symmetrical, inverted funnel shape indicates that publication bias is unlikely
- Conversely, an asymmetrical funnel indicates a relationship between treatment effect and study size. This indicates either publication bias or a systematic difference between smaller and larger studies ('small study effects')

Central Limit Theorem (CLT): the random sampling distribution of mean would always tend to be normal irrespective of the population distribution for which the sample were drown.

The mean of the random sampling distribution of means is equal to the mean of the original population

---

Confidence Interval (CI): describes the range of value around a mean, an odds ratio, a pvalue or a standard deviation within which the true value lies.

95% CI → 5% chance the true mean value for variable lies outside the range

CI = mean ± 2xSE (Standard Error)

Normal Distribution is also known as Gaussian distribution or 'bell-shaped' distribution. It describes the spread of many biological and clinical measurements

Properties of the Normal Distribution

- Symmetrical i.e. Mean = Median = Mode
- 68.3% of values lie within 1 SD of the mean
- 95.4% of values lie within 2 SD of the mean
- 99.7% of values lie within 3 SD of the mean
- This is often reversed, so that within 1.96 SD of the mean lie 95% of the sample values
- The range of the mean - (1.96 *SD) to the mean + (1.96 * SD) is called the 95% confidence interval, i.e. if a repeat sample of 100 observations are taken from the same group 95 of them would be expected to lie in that range

Standard deviation

- The standard deviation (SD) represents the average difference each observation in a sample lies from the sample mean
- SD = square root (variance)

Example: A study is performed to find the normal reference range for IgE levels in adults. Assuming IgE levels follow a normal distribution, what percentage of adults will have an IgE level above 2 standard deviations from the mean?

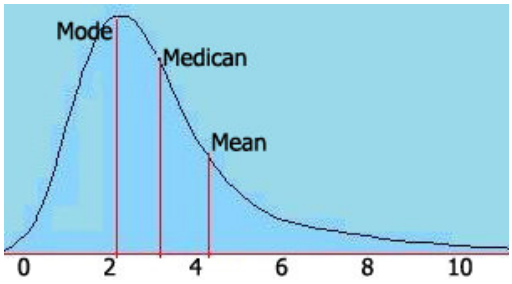
For normally distributed data 95.4% of values lie within 2 standard deviations of the mean, leaving 4.6% outside this range. Therefore 2.3% of values will be higher and 2.3% will be lower than 2 standard deviations from the mean. This figure is sometimes approximated to 2.5%

Skewed distributions

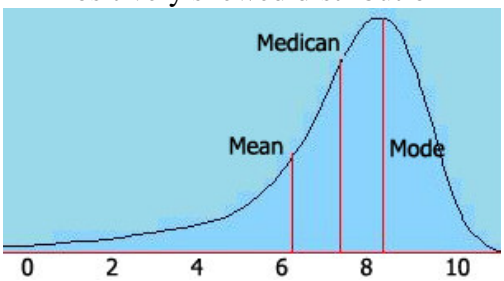
- Alphabetical order: mean - median - mode
- '>' For positive, '<' for negative

Skewed Distributions

- Normal distributions: mean = median = mode
- Positively skewed distribution: mean > median > mode
- Negatively skewed distribution mean < median < mode
- To remember the above note how they are in alphabetical order, think positive going forward with '>', whilst negative going backwards '<'



Positively skewed distribution



Negatively skewed distribution

Standard error of the mean = standard deviation / square root (number of patients)

The Standard Error of the Mean (SEM) is a measure of the spread expected for the mean of the observations - i.e. how 'accurate' the calculated sample mean is from the true population mean

Key point

- SEM = S / square root (n)
- Where S = standard deviation and n = sample size

$$SE_{\bar{x}} = \frac{s}{\sqrt{n}}$$

Therefore the SEM gets smaller as the sample size (n) ↑

A confidence interval for the mean can be calculated in a similar way to that for a single observation i.e. the 95% confidence interval = mean - (1.96 *SEM) to the mean + (1.96 * SEM)

Relative Risk (RR) is the ratio of risk in the experimental group (experimental event rate, EER) to risk in the control group (control event rate, CER)

To recap

- CER = rate at which events occur in the control group
- EER = rate at which events occur in the experimental group

Control event rate = (Number who had particular outcome with the control) / (Total number who had the control)

Experimental event rate = (Number who had particular outcome with the intervention) / (Total number who had the intervention)

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	Total number of patients	Experienced significant pain
Paracetamol	80	20
Placebo	100	80

Experimental event rate, EER = 20 / 80 = 0.25
Control event rate, CER = 80 / 100 = 0.8
Therefore the relative risk = EER / CER = 0.25 / 0.8 = 0.3125

Absolute risk reduction = (Control event rate) - (Experimental event rate)

Relative risk reduction (RRR) is calculated by dividing the absolute risk reduction by the control event rate

Using the above data, RRR = (CER - EER) / CER = (0.8 - 0.25) / 0.8 = 0.6875

Relative Risk	EER/CER
Absolute Risk Reduction	CER - EER
Relative Risk Reduction	(CER-EER) / CER

The Hazard Ratio (HR) is similar to relative risk but is used when risk is not constant to time. It is typically used when analysing survival over time

NNT = 1 / (CER - EER), or 1 / Absolute Risk Reduction

Numbers Needed to Treat and Absolute Risk Reduction

Numbers needed to treat (NNT) is a measure that indicates how many patients would require an intervention to ↓ the expected number of outcomes by 1. It is rounded to the next highest whole number

A new drug is trialled for the treatment of lung cancer. Drug A is given to 500 people with early stage non-small cell lung cancer and a placebo is given to 450 people with the same condition. After 5 years 200 people who received drug A had died compared to 225 who received the placebo. What is the number needed to treat to prevent one death?
Control (placebo) event rate = 225 / 450 = 0.5
Experimental (drug A) event rate = 200 / 500 = 0.4
Absolute risk reduction = 0.5 - 0.4 = 0.1
Number needed to treat = 1 / 0.1 = 10

Odds - remember a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome, NOT TO THE TOTAL NUMBER OF PEOPLE

Odds Ratio may be defined as the ratio of the odds of a particular outcome with experimental treatment and that of control

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	Total number of patients	Achieved = 50% pain relief
Paracetamol	60	40
Placebo	90	30

The odds of achieving significant pain relief with paracetamol = 40 / 20 = 2
The odds of achieving significant pain relief with placebo = 30 / 60 = 0.5
Therefore the odds ratio = 2 / 0.5 = 4 (experimental/control)

Pre- and Post- Test Odds and Probability

Pre-test probability = Prelivence of a condition
The proportion of people with the target disorder in the population at risk at a specific time (point prevalence) or time interval (period prevalence)
For example, the prevalence of rheumatoid arthritis in the UK is 1%

Post-test probability
The proportion of patients with that particular test result who have the target disorder
Post-test probability = post test odds / (1 + post-test odds)

Pre-test odds
The odds that the patient has the target disorder before the test is carried out
Pre-test odds = pre-test probability / (1 - pre-test probability)

Post-test odds
The odds that the patient has the target disorder after the test is carried out
Post-test odds = pre-test odds x likelihood ratio

Where the likelihood ratio for a positive test result = sensitivity / (1 - specificity)

Incidence and Prevalence: These two terms are used to describe the frequency of a condition in a population.

The **incidence** is the number of new cases per population in a given time period.

For example, if condition X has caused 40 new cases over the past 12 months per 1,000 of the population the annual incidence is 0.04 or 4%.

The **prevalence** is the total number of cases per population at a particular point in time.

For example, imagine a questionnaire is sent to 2,500 adults asking them how much they weigh. If from this sample population of 500 of the adults were obese then the prevalence of obesity would be 0.2 or 20%.

Relationship

- prevalence = incidence * duration of condition
- In chronic diseases the prevalence is much greater than the incidence
- In acute diseases the prevalence and incidence are similar. For conditions such as the common cold the incidence may be greater than the prevalence

Sensitivity and Specificity

Definitions

Imagine a scenario where people are tested for a disease. The test outcome can be positive (sick) or negative (healthy), while the actual health status of the persons may be different. In that setting:

- True positive: Sick people correctly diagnosed as sick
- False positive: Healthy people wrongly identified as sick
- True negative: Healthy people correctly identified as healthy
- False negative: Sick people wrongly identified as healthy

$$\text{sensitivity} = \frac{\text{number of True Positives}}{\text{number of True Positives} + \text{number of False Negatives}}$$

A sensitivity of **100%** means that the test recognizes all sick people as such. Thus in a high sensitivity test, a negative result is used to rule out the disease.

Sensitivity alone does not tell us how well the test predicts other classes (that is, about the negative cases). In the binary classification, as illustrated above, this is the corresponding specificity test, or equivalently, the sensitivity for the other classes.

Sensitivity is not the same as the **positive predictive value** (ratio of true positives to combined true and false positives), which is as much a statement about the proportion of actual positives in the population being tested as it is about the test.

The calculation of sensitivity does not take into account indeterminate test results. If a test cannot be repeated, the options are to exclude indeterminate samples from analysis (but the number of exclusions should be stated when quoting sensitivity), or, alternatively, indeterminate samples can be treated as false negatives (which gives the worst-case value for sensitivity and may therefore underestimate it).

$$\text{specificity} = \frac{\text{number of True Negatives}}{\text{number of True Negatives} + \text{number of False Positives}}$$

A specificity of **100%** means that the test recognizes all healthy people as healthy. Thus a positive result in a high specificity test is used to confirm the disease. The maximum is trivially achieved by a test that claims everybody healthy regardless of the true condition. Therefore, the specificity alone does not tell us how well the test recognizes positive cases. We also need to know the sensitivity of the test to the class, or equivalently, the specificities to the other classes.

A test with a high specificity has a low Type I error rate.

Specificity is sometimes confused with the precision or the positive predictive value, both of which refer to the fraction of returned positives that are true positives. The distinction is critical when the classes are different sizes. A test with very high specificity can have very low precision if there are far more true negatives than true positives, and vice versa.

Increasing the cut-off of a positive test result will ↓ the number of false positives and hence ↑ the specificity

Sensitivity = TP / (TP + FN) how many of the sick patients can the test identify by %
Specificity = TN / (TN + FP) how many of the healthy patients can the test identify by %
Positive predictive value = TP / (TP + FP) how many of the test +ve samples are actually sick
Negative predictive value = TN / (TN + FN) how many of the test –ve samples are actually healthy
Likelihood ratio for a positive test result = sensitivity / (1 - specificity) remember to convert 80% to 0.8
Likelihood ratio for a negative test result = (1 - sensitivity) /specificity remember to convert 60% to 0.6
Positive and negative predictive values are prevalence dependent. Likelihood ratios are not prevalence dependent

Screening: Wilson and Junger Criteria

1. The condition should be an important public health problem
2. There should be an acceptable treatment for patients with recognised disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognised latent or early symptomatic stage
5. The natural history of the condition, including its development from latent to declared disease should be adequately understood
6. There should be a suitable test or examination
7. The test or examination should be acceptable to the population
8. There should be agreed policy on whom to treat
9. The cost of case-finding (including diagnosis and subsequent treatment of patients) should be economically balanced in relation to the possible expenditure as a whole
10. Case-finding should be a continuous process and not a 'once and for all' project

Correlation and Linear Regression

Two measurements, or variables, may be plotted on a scatter plot. For example, age may be marked along the x axis and systolic blood pressure along the y axis

Correlation

The correlation coefficient (sometimes referred to as Pearson's product-moment coefficient) indicates how closely the points lie to a line drawn through the plotted data. It is denoted by the value R which

may lie anywhere between -1 and 1.

For example

- R = 1 - strong positive correlation (e.g. Systolic blood pressure always ↑ with age)
- R = 0 - no correlation (e.g. There is no correlation between systolic blood pressure and age)
- R = - 1 - strong negative correlation (e.g. Systolic blood pressure always ↓ with age)

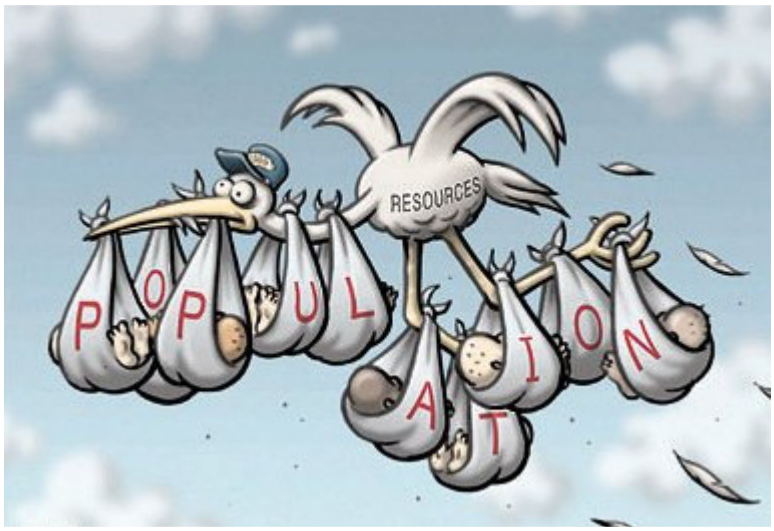
Whilst correlation coefficients give information about how one variable may ↑ or ↓ as another variable ↑ they do not give information about how much the variable will change. They also do not provide information on cause and effect

Linear regression

In contrast to the correlation coefficient, linear regression may be used to predict how much one variable changes when a second variable is changed. A regression equation may be formed:

Y = A + BX, where

- Y = the variable being calculated
- A = the intercept value, when x = 0
- B = the slope of the line or regression coefficient. Simply put, how much y changes for a given change in x
- X = the second variable



Study Design

The following table highlights the main features of the different types of study

Randomised controlled trial	Participants randomly allocated to intervention or control group (e.g. standard treatment or placebo) • Practical or ethical problems may limit use
Cohort study	Two (or more) are selected according to their exposure to a particular agent (e.g. medicine, toxin) and followed up to see how many develop a disease or other outcome • The usual outcome measure is the relative risk. • Examples include Framingham Heart Study
Case-control study	Patients with a particular condition (cases) are identified and matched with controls. Data is then collected on past exposure to a possible causal agent for the condition • Inexpensive, produce quick results • Useful for studying rare conditions • Prone to confounding
Cross-sectional survey	• Provide a 'snapshot', sometimes called prevalence studies • Provide weak evidence of cause and effect

Randomized Controlled Trial (RCT) involves the random allocation of different interventions (treatments or conditions) to subjects. As long as the numbers of subjects are sufficient, randomization is an effective method for balancing confounding factors between treatment groups

Randomized treatment prevents systemic diference between treatment groups

Cohort Study is done for a group of people who share a common characteristic or experience within a defined period (e.g., are born, leave school, lose their job, are exposed to a drug or a vaccine, etc.). Thus a group of people who were born on a day or in a particular period, say 1948, form a birth cohort. The comparison group may be the general population from which the cohort is drawn, or it may be another cohort of persons thought to have had little or no exposure to the substance under investigation, but otherwise similar. Alternatively, subgroups within the cohort may be compared with each other

Case-Control is a type of epidemiological study design. Case-control studies are used to identify factors that may contribute to a medical condition by comparing subjects who have that condition (the 'cases') with patients who do not have the condition but are otherwise similar (the 'controls')

Cross-Sectional Studies (also known as Cross-sectional analysis) form a class of research methods that involve observation of some subset of a population of items all at the same time, in which, groups can be compared at different ages with respect of independent variables, such as IQ and memory. The fundamental difference between cross-sectional and **longitudinal studies** is that cross-sectional studies take place at a single point in time and that a longitudinal study involves a series of measurements taken over a period of time. **Both are a type of observational study**. Cross-sectional studies are used in most branches of science, in the social sciences and in other fields as well. Cross-sectional research takes a 'slice' of its target group and bases its overall finding on the views or behaviours of those targeted, assuming them to be typical of the whole group.

Study Design: Evidence and Recommendations

Levels of evidence

- Ia - evidence from meta-analysis of randomised controlled trials
- Ib - evidence from at least one randomised controlled trial
- IIa - evidence from at least one well designed controlled trial which is not randomised
- IIb - evidence from at least one well designed experimental trial
- III - evidence from case, correlation and comparative studies
- IV - evidence from a panel of experts

Grading of recommendation

- Grade A - based on evidence from at least one randomised controlled trial (i.e. Ia or Ib)
- Grade B - based on evidence from non-randomised controlled trials (i.e. IIa, IIb or III)
- Grade C - based on evidence from a panel of experts (i.e. IV)

Study Design: New Drugs

When a new drug is launched there are a number of options available in terms of study design. One option is a placebo controlled trial. Whilst this may provide robust evidence it may be considered unethical if established treatments are available and it also does not provide a comparison with standard treatments.

Superiority Trial → Large Sample Size Needed

If a drug is therefore to be compared to an existing treatment a statistician will need to decide whether the trial is intended to show superiority, equivalence of non-inferiority.

- Superiority: whilst this may seem the natural aim of a trial one problem is the large sample size needed to show a significant benefit over an existing treatment
- Equivalence: an equivalence margin is defined (-delta to +delta) on a specified outcome. If the confidence interval of the difference between the two drugs lies within the equivalence margin then the drugs may be assumed to have a similar effect
- Non-inferiority: similar to equivalence trials but only the lower confidence interval needs to lie within the equivalence margin (i.e. -delta). Small sample sizes are needed for these trials. Once a drug has been shown to be non-inferior large studies may be performed to show superiority

It should be remembered that drug companies may not necessarily want to show superiority over an existing product. If it can be demonstrated that their product is equivalent or even non-inferior then they may compete on price or convenience.

Intention to treat analysis is a method of analysis for randomized controlled trials in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment. Intention to treat analysis is done to avoid the effects of crossover and drop-out, which may affect the randomization to the treatment groups

MISCELLANEOUS

Altitude Related Disorders: there are three main types of altitude related disorders: acute mountain sickness (AMS), which may progress to high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE). All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes

Acute mountain sickness is generally a self-limiting condition. Features of AMS start to occur above 2,500 - 3,000m, developing gradually over 6-12 hours and potentially last a number of days:

- Headache
- Nausea
- Fatigue

Prevention and treatment of AMS

- The risk of AMS may actually be positively correlated to physical fitness
- Gain altitude at no more than 500 m per day
- **Acetazolamide** (a carbonic anhydrase inhibitor) is widely used to prevent AMS and has a supporting evidence base
- Treatment: descent

A minority of people above 4,000m go onto develop high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE), potentially fatal conditions

- HAPE presents with classical pulmonary edema features
- HACE presents with headache, ataxia, papilledema

Management of HACE

- Descent
- Dexamethasone

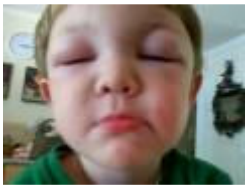
Management of HAPE

- Descent
- Dexamethasone, nifedipine, phosphodiesterase type V inhibitors (Sildenafil)
- Oxygen if available

Hereditary Angioedema is an autosomal dominant condition associated with low plasma levels of the C1 inhibitor (C1-INH) protein. C1-INH is a multifunctional serine protease inhibitor - the probable mechanism behind attacks is uncontrolled release of bradykinin resulting in edema of tissues

Investigation

- C1-INH level is low
- Low C2 and C4 levels are seen, even between attacks



Symptoms

- Attacks may be proceeded by painful macular rash
- Painless, non-pruritic swelling of subcutaneous/submucosal tissues
- May affect upper airways, skin or abdominal organs (can occasionally present as abdominal pain due to visceral edema)
- Urticaria is not usually a feature

Management

- Acute: IV C1-inhibitor concentrate or FFP
- Anabolic steroid; Danazol may help

Galactosemia is a rare autosomal recessive condition caused by the absence of galactose-1-phosphate uridyl transferase. This results in intracellular accumulation of galactose-1-phosphate

Features

- Jaundice
- Failure to thrive
- Hepatomegaly
- Cataracts
- Hypoglycemia after exposure to galactose
- Fanconi syndrome

Diagnosis

- Urine reducing substances

Management is with a galactose free diet

DVT Risk Factors:

Hematological

- Thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
- Polycythemia
- Paroxysmal nocturnal hemoglobinuria
- Hyperviscosity syndrome

Autoimmune

- Antiphospholipid syndrome
- Behcet's

Drugs

- Combined oral contraceptive pill: 3rd generation more than 2nd generation
- Antipsychotics (especially olanzapine) have recently been shown to be a risk factor

Other conditions

- Homocystinuria

Management of Confusion:

Underlying causes of confusion need to be looked for and treated as appropriate, for example hypercalcemia, infection, urinary retention and medication. If specific treatments fail then the following may be tried:

- First choice: haloperidol
- Other options: chlorpromazine, levomepromazine

In the terminal phase of the illness (for example a patient on the Care of the Dying pathway) then agitation or restlessness is best treated with midazolam

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Motion sickness - hyoscine > cyclizine > promethazine

Motion sickness describes the nausea and vomiting which occurs when an apparent discrepancy exists between visually perceived movement and the vestibular systems sense of movement.

Management

- The BNF recommends hyoscine (e.g. Transdermal patch) as being the most effective treatment. Use is limited due to side-effects
- Non-sedating antihistamines such as cyclizine or cinnarizine are recommended in preference to sedating preparation such as promethazine

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AIP - porphobilinogen de**A**minase - P**C**T - uroporphyrinogen de**C**arboxylase

Porphyrias

Overview

- Abnormality in enzymes responsible for the biosynthesis of heme.
- Results in overproduction of intermediate compounds (porphyrins)
- May be acute or non-acute
- All Porphyrias has autosomal dominant inheritance excpet congenital porphyrias (recessive)
- Only the acute porphyrias develop neurological consequences
- All porphyrias are photosensitive except AIP
- If it's inherited or congenital it's extremely rare (unlikely to be the answer)
- Urinary porphyria is ↑ in all the 3 types
- Fecal porphyria is ↑ in Variegate porphyria and hereditary porphyrias

Acute intermittent porphyria (AIP) (Acute)

- Autosomal dominant
- Defect in porphobilinogen deAminase
- Results accumulation of delta aminolaevulinic acid and porphobilinogen
- ♀s, 20-40 year olds more likely to be affected (♀5:1)
- Typically present with abdominal symptoms, neuropsychiatric symptoms
- Hypertension and tachycardia common
- Urine turns deep red on standing

Features

- Abdominal: abdominal pain, vomiting
- Neurological: motor neuropathy
- Psychiatric: e.g. Depression
- Hypertension and tachycardia common
- No feces porphyria (can not be detected in stool)

Diagnosis

- Classically urine turns deep red on standing
- Raised urinary porphobilinogen (elevated between attacks and to a greater extent during acute attacks)
- Assay of red cells for porphobilinogen deaminase
- Raised serum levels of delta aminolaevulinic acid and porphobilinogen

Management:

- Hematin: needs to be given very early in an attack to be effective. Effectiveness varies among individuals. They are not curative drugs, but can shorten attacks and reduce the intensity of an attack

Porphyria cutanea tarda (PCT) (Non-acute)

- Most common hepatic porphyria
- 80% sporadic and 20% autosomal dominant
- No neurological consequences only urine porphyria
- The exact frequency is not clear because many people with PCT never experience symptoms
- Defect in uroporphyrinogen decarboxylase
- May be caused by hepatocyte damage e.g. Alcohol, estrogens
- Classically photosensitive rash with bullae, skin fragility on face and dorsal aspect of hands
- Urine: elevated uroporphyrinogen and pink fluorescence of urine under wood's lamp
- Manage with chloroquine

Variegate porphyria (Acute)

- Autosomal dominant
- Defect in protoporphyrinogen oxidase
- Photosensitive blistering rash
- Abdominal and neurological symptoms
- More common in south africans

Kartagener's syndrome (also known as primary ciliary dyskinesia) was first described in 1933 and most frequently occurs in examinations due to its association with dextrocardia (e.g. 'quiet heart sounds', 'small volume complexes in lateral leads')

Features

- Dextrocardia or complete situs inversus
- Bronchiectasis
- Recurrent sinusitis
- Subfertility (secondary to diminished sperm motility and defective ciliary action in the fallopian tubes)

Superior Vena Caval Obstruction (SVCO) is an uncommon manifestation of mediastinal masses, but it is particularly for small-cell lung cancer.

Treatment depends on the cause and pace of the progression of symptoms.

- Although SVCO is an emergency in the presence of airway compromise, where possible it is important to get tissue for a histological diagnosis, as some tumours are better treated with chemotherapy than radiotherapy. In this case, if feasible, a bronchoscopy would probably provide tissue for a diagnosis.
- For most tumours, radiotherapy is a good treatment and relieves symptoms in 90% of patients within 2 weeks.
- Patients should be sat up and given oxygen to provide initial relief.
- In severe cases high-dose steroids can be helpful.
- For patients with recurrent SVCO, insertion of expandable wire stents under radiological guidance provides relief in a high proportion of patients.

Amyloidosis: variety of conditions whereby body produces "bad proteins", (amyloid proteins), which are abnormally deposited in tissues. A protein is described as being amyloid if, due to an alteration in its secondary structure, it takes on a particular aggregated insoluble form. Symptoms vary widely depending upon the site of amyloid deposition. Amyloidosis may be inherited or acquired; acquired form is associated with long standing chronic illnesses (DM, Rheumatoid Arthritis).

Diagnosis:

- **Biopsy** of abdominal wall fat, the **rectum** or a salivary gland can be examined for evidence of characteristic amyloid deposits. The tissue is treated with Congo red stain, which combined with polarized light makes the amyloid proteins appear apple-green on microscopy.
- Abdominal wall fat biopsy is not completely sensitive, and sometimes biopsy of an involved organ (such as the kidney) is required to achieve a diagnosis
- The nature of the amyloid protein (type) can be determined by various ways:
    - Protein electrophoresis or light chain determination
    - Binding of particular antibodies to the amyloid found in the tissue
    - Extraction of the protein and identification of its individual amino acids

Types:

- AL amyloid
    - L for immunoglobulin Light chain fragment
    - Due to myeloma, Waldenstrom's, MGUS
    - Features include: cardiac and neurological involvement, macroglossia, periorbital eccymoses

Part II Tip

Management of AL type:

- The most effective treatment is autologous bone marrow transplants with stem cell rescues. However many patients are too weak to tolerate this approach
- Other treatments can involve application of chemotherapy similar to that used in multiple myeloma. A combination of bortezomib and dexamethasone has been proposed, as has melphalan and dexamethasone.
- Digoxin is contraindicated in cardiac amyloidosis (restrictive cardiomyopathy)

- AA amyloid
    - A for precursor serum amyloid A protein, an acute phase reactant
    - Seen in chronic infection/inflammation
    - E.g. TB, bronchiectasis, rheumatoid arthritis
    - Features: renal involvement most common feature

- β-2 microglobulin amyloidosis
    - Precursor protein is β-2 microglobulin, part of the major histocompatibility complex
    - Associated with patients on renal dialysis

Cardiac amyloidosis most commonly presents as restrictive cardiomyopathy, associated with AL Amyloidosis

Presentation:

- Typical presentation of right heart failure:
    - Jugular venous distension
    - Peripheral oedema
    - Orthopnoea and paroxysmal nocturnal dyspnea are typically absent
- In more advanced stages systolic dysfunction also occurs

Diagnosis:

- Combination of low-voltage ECG and thickened ventricular walls is one of the characteristic features of cardiac amyloidosis.
- Echocardiographic abnormalities include dilatation of atria, thickened interatrial septum, diastolic dysfunction and small-volume ventricles. The most distinctive feature of cardiac amyloidosis is a **sparkling**, granular **appearance of myocardium**, but this is a relatively insensitive feature occurring only in about 25% of cases.

POEMS Syndrome:

Polyneuropathy, **O**rganomegaly, **E**ndocrinopathy or **E**dema, **M**-protein and **S**kin abnormalities (including hyperpigmentation and hypertrichosis), also known as Crow–Fukase syndrome, Takatsuki disease. It is a rare syndrome, defined as the combination of a plasma-cell proliferative disorder (typically myeloma), polyneuropathy and organomegaly. Average age of onset is 50 years, ♂:♀ 2:1. Its 5 years survival is 60% if untreated

Pathophysiology: is not known, however, ↑ cytokines and growth factors have been implicated.

Presentation:

- Polyneuropathy: bilateral symmetric disturbance, involves both motor and sensory nerves, begins distally, and has a progressive proximal spread. No cranial or autonomic nerves involvement. Both demyelination and axonal degeneration are noted.
- Organomegaly: liver, lymph nodes, and spleen are most frequently involved.
- Multiple endocrinopathies, most patients have more than one endocrine abnormality.
- POEMS syndrome is seen in the setting of a plasma cell dyscrasia. Although many plasma cell disorders have been reported in patients with POEMS syndrome, most patients are seen with osteosclerotic myeloma or monoclonal gammopathy of unknown significance (MGUS). Classic multiple myeloma has not been associated with the disease.

Management:

- No treatment was found, just correct the hematological abnormality
- Conventional treatments for demyelinating neuropathy (Steroids, IV immunoglobulin and plasma exchange) are ineffective; treatment must be aimed at the hematological disorder.

Systemic Mastocytosis

results from a neoplastic proliferation of mast cells

Features

- Urticaria pigmentosa - produces a wheal on rubbing (Darier's sign)
- Flushing
- Abdominal pain
- Monocytosis on the blood film

Diagnosis

- Raised serum tryptase levels
- Urinary histamine

Cancers in UK: (excludes non-melanoma skin cancer):

Most common causes of cancer	Most common causes of death from cancer
• Breast • Lung • Colorectal • Prostate • Bladder • Non-Hodgkin's lymphoma • Melanoma • Stomach • Esophagus • Pancreas	• Lung • Colorectal • Breast • Prostate • Esophagus • Stomach • Bladder • Non-Hodgkin's lymphoma • Ovarian • Leukemia

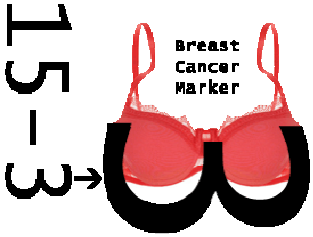
Tumor markers may be divided into:

- Monoclonal antibodies against carbohydrate or glycoprotein tumor antigens
- Tumor antigens
- Enzymes (alkaline phosphatase, neuron specific enolase)
- Hormones (e.g. calcitonin, ADH)

It should be noted that tumor markers usually have a low specificity

Monoclonal antibodies

Tumor marker	Association
CA 125	Ovarian cancer
CA 19-9	Pancreatic cancer
CA 15-3	Breast cancer



Tumor antigens

Tumor marker	Association
Prostate specific antigen (PSA)	Prostatic carcinoma
α -feto protein (AFP)	Hepatocellular carcinoma, teratoma
Carcinoembryonic antigen (CEA)	Colorectal cancer

Patients with Sjogren's syndrome have an ↑ risk of lymphoid malignancies

Thymomas are the most common tumor of the anterior mediastinum

Associated with

- Myasthenia gravis (30-40% of patients with thymoma)
- **Red Cell Aplasia**
- Dermatomyositis
- Also : SLE, SIADH

Causes of death

- Compression of airway
- Cardiac tamponade

Testicular choriocarcinomas: are rare.

Diagnosis:

- Primary tumour can be very small and go undetected on testicular examination.
- Marked ↑ in β-HCG in the presence of a normal AFP and CEA.
- Scrotal ultrasound is used to support the diagnosis
- CTs are of significant value for staging.

Management:

- Choriocarcinoma is extremely sensitive to cisplatin based chemotherapy, with cure rates of up to 80% being achievable, even in advanced disease.

Otitis externa is a common reason for primary care attendance in the UK.

Causes of otitis externa include:

- Infection: bacterial (Staphylococcus aureus, Pseudomonas aeruginosa) or fungal
- Seborrhoeic dermatitis
- Contact dermatitis (allergic and irritant)

Pseudomonas aeruginosa causes malignant otitis externa

Features

- Ear pain, itch, discharge
- Otoscopy: red, swollen, or eczematous canal

The recommend initial **management of otitis externa** is:

- Topical antibiotic or a combined topical antibiotic with steroid
- **If the tympanic membrane is perforated aminoglycosides should not be used**
- If there is canal debris then consider removal
- If the canal is extensively swollen then an ear wick is sometimes inserted

Second line options include

- Consider contact dermatitis secondary to neomycin
- Oral antibiotics if the infection is spreading
- Taking a swab inside the ear canal
- Empirical use of an antifungal agent

Malignant otitis externa is more common in elderly diabetics. In this condition there is extension of infection into the bony ear canal and the soft tissues deep to the bony canal. Intravenous antibiotics may be required.

Meniere's disease is a disorder of the inner ear of unknown cause. It is characterized by excessive pressure and progressive dilation of the endolymphatic system. It is more common in middle-aged adults but may be seen at any age. Meniere's disease has a similar prevalence in both men and women.

Features

- Recurrent episodes of vertigo, tinnitus and hearing loss (sensorineural). Vertigo is usually the prominent symptom
- A sensation of aural fullness or pressure is now recognised as being common
- Other features include nystagmus and a positive Romberg test (patient can't stand-alone when eyes closed and feet together)
- Episodes last minutes to hours

Natural history

- Symptoms resolve in the majority of patients after 5-10 years
- Some patients may be left with hearing loss
- Psychological distress is common

Management

- ENT assessment is required to confirm the diagnosis
- Patients should inform the DVLA. The current advice is to cease driving until satisfactory control of symptoms is achieved
- Acute attacks: buccal or intramuscular prochlorperazine. Admission is sometimes required
- Prevention: betahistine may be of benefit

Rinne's and Weber's tests allows differentiation of conductive and sensorineural deafness

Rinne's test

- Tuning fork is placed over mastoid process, followed by repositioning just over external acoustic meatus
- Air conduction (AC) is normally better than bone conduction (BC)
- If BC > AC then conductive deafness

Weber's test

- Tuning fork is placed over middle of forehead, patient is asked which side is loudest
- In unilateral **sensorineural** deafness, sound is localised to the '**good**' side
- In unilateral **conductive** deafness, sound is localised to the '**bad**' side

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Tinnitus:

Causes include:

Meniere's Disease	**Associated with hearing loss, tinnitus and sensation of fullness or pressure in one or both ears, Vertigo is the prominent symptom**
Otosclerosis	Onset is usually at 20-40 years Conductive deafness Tinnitus Normal tympanic membrane* Positive family history
Acoustic neuroma	Hearing loss, vertigo, tinnitus Absent corneal reflex is important sign Associated with neurofibromatosis type 2
Hearing loss	Causes include excessive loud noise and presbycusis
Drugs	Aspirin Aminoglycosides Loop diuretics Quinine

Other causes include

- Impacted ear wax
- Chronic suppurative otitis media

*10% of patients may have a 'flamingo tinge', caused by hyperaemia

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Ramsay Hunt syndrome: (herpes zoster oticus) is caused by the reactivation of the varicella zoster virus in the geniculate ganglion of the seventh cranial nerve.

Features

- Auricular pain is often the first feature
- Facial nerve palsy
- Vesicular rash around the ear
- Other features include vertigo and tinnitus

Management

- oral aciclovir and corticosteroids are usually given

Hyperhidrosis: describes the excessive production of sweat

Management options include

- Topical aluminium chloride preparations are first-line. Main side effect is skin irritation
- Iontophoresis: particularly useful for patients with palmar, plantar and axillary hyperhidrosis
- Botulinum toxin: currently licensed for axillary symptoms
- Surgery: e.g. endoscopic transthoracic sympathectomy. Patients should be made aware of the risk of compensatory sweating

Benign paroxysmal positional vertigo (BPPV) is one of the most common causes of vertigo encountered. It is characterized by the sudden onset of dizziness and vertigo triggered by changes in head position

Features

- Vertigo triggered by change in head position (e.g. Rolling over in bed or gazing upwards)
- May be associated with nausea
- Each episode typically lasts 10-20 seconds
- Positive halpike manoeuvre

BPPV has a good prognosis and usually resolves spontaneously after a few weeks to months.

Symptomatic relief may be gained by:

- Epley maneuvre (successful in around 80% of cases)

Medication is often prescribed (e.g. betahistine) but it tends to be of limited value

Indications for plasma exchange

- ANCA positive vasculitis e.g. Wegener's, Churg-Strauss
- Cryoglobulinemia
- Goodpasture's syndrome
- Guillain-Barre syndrome
- Hyperviscosity syndrome e.g. Secondary to myeloma
- Myasthenia gravis
- TTP/HUS

Cerebral malaria is not a standard indication for plasma exchange. Exchange transfusions have been tried but it is generally only justified when peripheral parasitemia is greater than 10% of circulating erythrocytes. The role of blood transfusions remains controversial, as they are both expensive and potentially dangerous in many malaria areas

Macroglossia

Causes

- Hypothyroidism
- Acromegaly
- Amyloidosis
- Duchenne muscular dystrophy
- Mucopolysaccharidosis (e.g. Hurler syndrome)

Patients with Down's syndrome are now thought to have apparent macroglossia due to a combination of mid-face hypoplasia and hypotonia

Alpha-1 Antitrypsin (A1AT) Deficiency is a common inherited condition caused by a lack of a protease inhibitor (Pi) normally produced by the liver

Genetics

- Located on chromosome 14
- A1AT deficiency is inherited in an autosomal recessive **/co-dominant** fashion
- Alleles classified by their electrophoretic mobility - M: normal, S: slow, and Z: very slow
- Normal = PiMM
- Homozygous PiSS (50% normal A1AT levels)
- Homozygous PiZZ (10% normal A1AT levels)

Features

- Patients who manifest disease usually have PiZZ genotype
- Lungs: panacinar emphysema, most marked in lower lobes
- Liver: cirrhosis and hepatocellular carcinoma in adults, cholestasis in children

Investigations

- A1AT concentrations

Management

- No smoking
- Supportive: bronchodilators, physiotherapy
- Intravenous α1-antitrypsin protein concentrates
- Surgery: volume reduction surgery, lung transplantation

α 1-antitrypsin levels in the blood depend on the genotype. Some mutant forms fail to fold properly and are, thus, targeted for destruction in the proteasome, whereas others have a tendency to polymerise, being retained in the endoplasmic reticulum. The serum levels of some of the common genotypes are:

Analysis

- PiMM: 100% (normal)
- PiMS: 80% of normal serum level of A1AT
- PiSS: 60% of normal serum level of A1AT
- PiMZ: 60% of normal serum level of A1AT.. Up to here, pts have a low risk of developing clinically evident lung disease
- PiSZ: 40% of normal serum level of A1AT
- PiZZ: 10-15% (severe α 1-antitrypsin deficiency)

PiZ is caused by a glutamate to lysine mutation at position 342
PiS is caused by a glutamate to valine mutation at position 264

Lymphadenopathy: there are many causes of generalised lymphadenopathy

Infective	Neoplastic	Others
• Infectious mononucleosis • HIV, including seroconversion illness • Eczema with secondary infection • Rubella • Toxoplasmosis • CMV • Tuberculosis • Roseola infantum	• Leukemia • Lymphoma	• Autoimmune conditions: SLE, rheumatoid arthritis • Graft versus host disease • Sarcoidosis • Drugs: phenytoin and to a lesser extent allopurinol, isoniazid

Fitness to Fly

UK Civil Aviation Authority (CAA) has issued guidelines on air travel for people with medical conditions;

Cardiovascular disease

- Unstable angina, uncontrolled hypertension, uncontrolled cardiac arrhythmia, decompensated heart failure, severe symptomatic valvular disease: **SHOULD NOT FLY**
- Uncomplicated myocardial infarction: may fly after 7-10 days
- Complicated myocardial infarction: after 4-6 weeks
- Coronary artery bypass graft (CABG): after 10-14 days
- Percutaneous coronary intervention (PCI): after 5 days

Respiratory disease

- Pneumonia: should be 'clinically improved with no residual infection'
- Pneumothorax: absolute contraindication, may travel 2 weeks after successful drainage if there is no residual air

Pregnancy

- Most airlines do not allow travel after 36 weeks for a single pregnancy and after 32 weeks for a multiple pregnancy
- Most airlines require a certificate after 28 weeks confirming that the pregnancy is progressing normally

Surgery

- Travel should be avoided for 10 days following abdominal surgery
- Laparoscopic surgery: after 24 hours
- Colonoscopy: after 24 hours
- Following the application of a plaster cast, the majority of airlines restrict flying for 24 hours on flights of less than 2 hours or 48 hours for longer flights

Hematological disorders

- Patients with a hemoglobin of greater than 8 g/dl may travel without problems

Reye's syndrome: is a severe, progressive encephalopathy affecting children that is accompanied by fatty infiltration of the liver, kidneys and pancreas. The aetiology of Reye's syndrome is not fully understood although there is a known association with aspirin use and a viral cause has been postulated.

The peak incidence is 2 years of age, **features include**:

- May be history of preceding viral illness
- Encephalopathy: confusion, seizures, cerebral oedema, coma
- Fatty infiltration of the liver, kidneys and pancreas
- Hypoglycaemia

Management is supportive
Prognosis is poor - 30-40% mortality

Clubbing

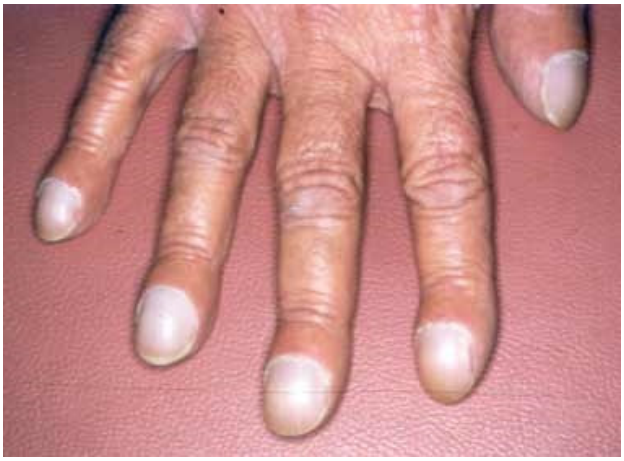
The causes of clubbing may be divided into cardiac, respiratory and other

Cardiac causes

- Cyanotic congenital heart disease (Fallot's, TGA)
- Bacterial endocarditis
- Atrial myxoma

Respiratory causes

- Lung cancer
- Pyogenic conditions: cystic fibrosis, bronchiectasis, abscess, empyema
- Asbestosis, mesothelioma
- Fibrosing alveolitis



Other causes

- Crohn's, to a lesser extent UC
- Cirrhosis, primary biliary cirrhosis
- Graves' disease (thyroid acropachy)
- Rare: Whipple's disease

Syncope may be defined as a transient loss of consciousness due to global cerebral hypoperfusion with rapid onset, short duration and spontaneous complete recovery. Note how this definition excludes other causes of collapse such as epilepsy.

The European Society of Cardiology published guidelines in 2009 on the investigation and management of syncope. They suggested the following classification:

Reflex syncope (neurally mediated)

- Vasovagal: triggeres; emotion, pain, stress or orthostatic factors. Often referred to as 'fainting'
- Situational: cough, micturition, gastrointestinal
- Carotid sinus syncope

Carotid sinus hypersensitivity (CSH): diagnosis is only made after ischemic heart disease or rhythm disturbance have been excluded. CSH may be predominantly cardioinhibitory (bradycardia), vasodilatory (hypotension), or a mixture of the two. Cardioinhibitory is usually managed with insertion of a dual-chamber pacemaker, and vasodilator is managed with support stockings, fludrocortisone and midodrine.

Orthostatic syncope

- Primary autonomic failure: Parkinson's disease, Lewy body dementia
- Secondary autonomic failure: e.g. Diabetic neuropathy, amyloidosis, uraemia
- Drug-induced: diuretics, alcohol, vasodilators
- Volume depletion: hemorrhage, diarrhoea

Cardiac syncope

- Arrhythmias: bradycardias (sinus node dysfunction, AV conduction disorders) or tachycardias (supraventricular, ventricular)
- Structural: valvular, myocardial infarction, hypertrophic obstructive cardimyopathy
- Others: pulmonary embolism

Reflex syncope is the most common cause in all age groups although orthostatic and cardiac causes become more common in older patients.

Evalulation

- Cardiovascular examination
- Postural blood pressure readings: a symptomatic fall in systolic BP > 20 mmHg or diastolic BP > 10 mmHg or decrease in systolic BP < 90 mmHg is considered diagnostic
- ECG
- Carotid sinus massage
- Tilt table test
- 24 hour ECG

Fibromyalgia is a syndrome characterized by widespread pain throughout the body with tender points at specific anatomical sites. The cause of fibromyalgia is unknown.

Epidemiology

- Women are 10 times more likely to be affected
- Typically presents between 30-50 years old

Features

- Pain: at multiple site, sometimes 'pain all over'
- Lethargy
- Sleep disturbance, headaches, dizziness are common

Diagnosis is clinical and sometimes refers to the American College of Rheumatology classification criteria which list 9 pairs of tender points on the body. If a patient is tender in at least 11 of these 18 points it makes a diagnosis of fibromyalgia more likely

The management of fibromyalgia is often difficult and needs to be tailored to the individual patient. A psychosocial and multidisciplinary approach is helpful. Unfortunately there is currently a paucity of evidence and guidelines to guide practice. The following is partly based on consensus guidelines from the European League against Rheumatism (EULAR) published in 2007.

- Explanation
- Exercise programme
- Cognitive behavioural therapy
- Anti-depressants: amitriptyline

Monoclonal Antibodies: have an increasing role in medicine. They are manufactured by a technique called somatic cell hybridization. This involves the fusion of myeloma cells with spleen cells from a mouse (recent advances: rabbit B-cells) that has been immunized with the desired antigen. The resulting fused cells are termed a hybridoma and act as a 'factory' for producing monoclonal antibodies. The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies (HAMAs). This problem is overcome by combining the variable region from the mouse antibody with the constant region from a human antibody.

Monoclonal antibodies are also used for:

- Medical imaging when combined with a radioisotope
- Identification of cell surface markers in biopsied tissue
- Diagnosis of viral infections

MONOCLONAL AB	TYPE	USES
Rituximab	Anti-CD20	non-Hodgkin's lymphoma
Infliximab	anti-**TNF**	rheumatoid arthritis and Crohn's
Cetuximab	anti epidermal growth factor receptor	metastatic colorectal cancer and head and neck cancer
Trastuzumab	anti-**HER**2, anti EGF receptor	metastatic **breast** cancer
Alemtuzumab	anti-CD52	chronic lymphocytic leukemia
abciximab	anti-glycoprotein IIb/IIIa receptor	undergoing PCI, prevention of ischemic events in patients
OKT3	anti-CD3	prevent organ rejection

Types of Transplants:

- Autograft: when the same individual acts as donor and recipient
- Isograft: when donor and recipient are genetically identical
- Allograft: when donor and recipient are genetically dissimilar but belong to same specimen
- Xenograft: when donor and recipient belong to different specimen
- Orthotopic transplant: when the transplanted part is placed in its normal anatomical location
- Heterotropic transplant: when the transplanted part is placed in different anatomical location

Post Cranial Irradiation Somnolence Syndrome: was first identified in patients treated with radiotherapy for scalp ringworm infection.

Features:

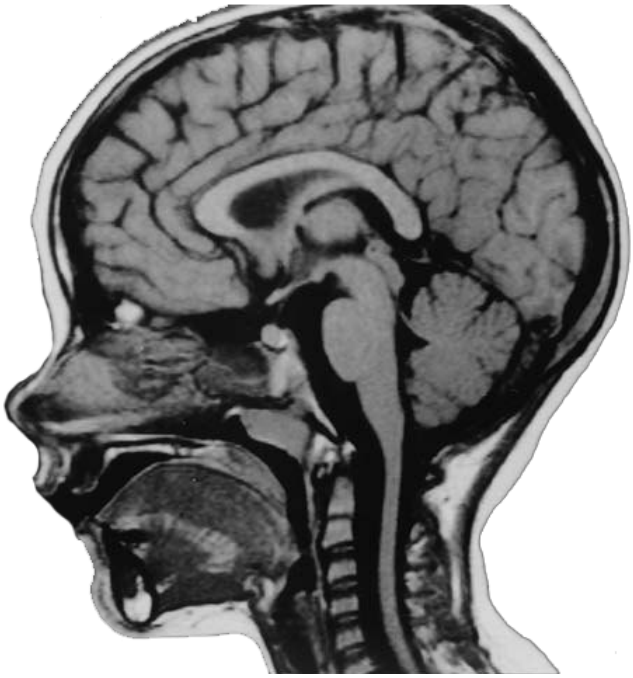
- Excessive somnolence
- Lethargy and clumsiness
- Tends to occur around 11-21 or 31-35 days after high dose cranial radiotherapy.
- No focal cause is identified and it is postulated that the condition may occur due to post irradiation demyelination.
- No specific therapy is required, some case reports suggest that corticosteroids may be of use but the evidence is not firmly established.

To differentiate it from cerebral mets or cerebral edema
There should be no new focal neurological signs in post irradiation SS.

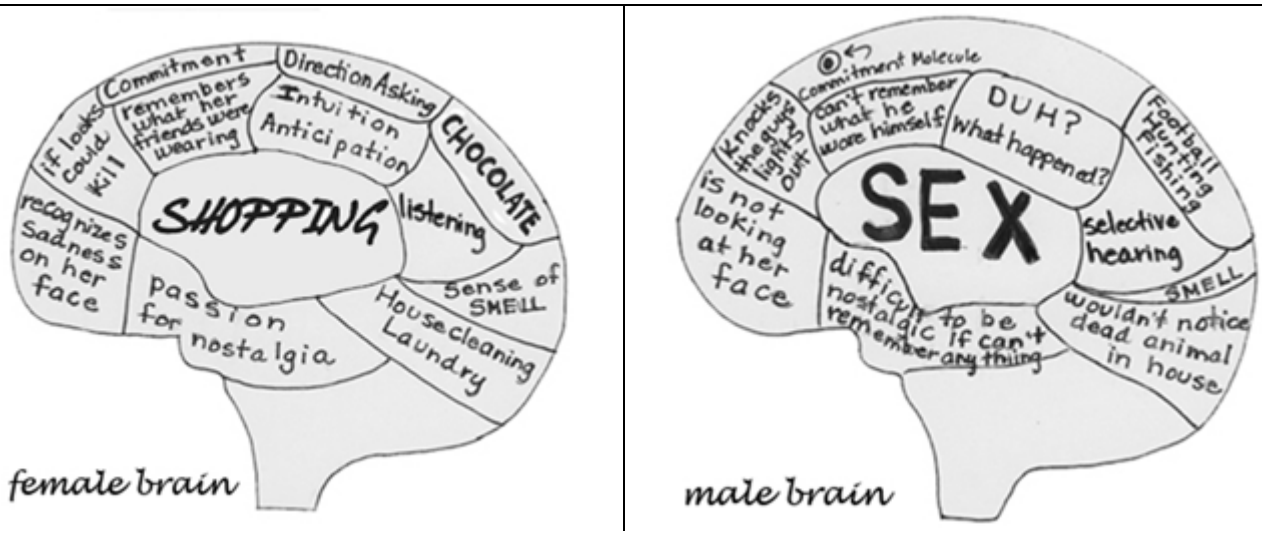
Condition	Gene	About
Acute myeloid leukemia	5: deletion 7: deletion	
Auto Dom Polycystic Kidney Disease	Type-I: 16 Type-II: 4	
α-1 antitrypsin (A1AT) deficiency	14	lack of a protease inhibitor (Pi)
α-thalassemia	16	deficiency of α chains in hemoglobin
Alzheimer's disease	21: amyloid precursor protein 14: presenilin-I 1: presenilin -II	most cases are sporadic 5% are inherited as an autosomal dominant
Autoimmune polyendocrinopathy syndrome	21	autosomal recessive
Cystic fibrosis (CF)	7	autosomal recessive
Cystinuria	2: SLC3A1 gene, 19: SLC7A9	autosomal recessive
familial adenomatous polyposis	5	autosomal dominant
Familial Motor neuron disease	21	superoxide dismutase deficiency
Friedreich's ataxia	9	autosomal recessive, **trinucleotide repeat disorder**
Hemochromatosis	6	autosomal recessive
HLA antigens	6	
Marfan's syndrome	15	autosomal dominant
Myotonic dystrophy	3: Type II 19: Type I	autosomal dominant **trinucleotide repeat disorder**
NF1	17	neurofibromatosis has 17 characters
NF2	22	
Noonan’s Syndrome	12	autosomal dominant
p53 gene	17p	tumour suppressor gene
Phenylketonuria (PKU)	12	autosomal recessive
Prader-Willi syndrome	15	Microdeletion of the paternal 15q11-13
Von Hippel-Lindau	3	autosomal dominant

Condition	Translocation	About
Burkitt's lymphoma	t(8;14)	MYC oncogene is translocated to an immunoglobulin gene
Chronic myeloid leukemia	t(9:22)	BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal Philadelphia chromosome95%
Mantle cell lymphoma	t(11;14)	deregulation of the cyclin D1 (BCL-1) gene
promyelocytic leukemia (M3)	t(15;17)	fusion of PML and RAR-α genes

NEUROLOGY



Sagittal MRI of the brain and spinal cord of a patient with Friedreich's ataxia, demonstrating spinal cord atrophy



Comparison between male and female brain

Cerebral lobe	Abnormality	
Frontal Lobe	• Difficulties with task sequencing • Difficulties with executive skills • Expressive aphasia (Broca's) : located in the posterior aspect of the frontal lobe, in the inferior frontal gyrus • Anosmia	• Primitive reflexes • Perseveration (repeatedly asking same question or doing same task) • Changes in personality • Inability to generate a list • Disinhibition
Parietal Lobe	• Apraxias: loss of the ability to execute learned purposeful movements • Neglect • Astereognosis (unable to recognise object by feeling) = tactile agnosia • Homonymous **inferior quadrantanopia** • Sensory inattention	• Acalculia: inability to perform mental arithmetic • Gerstmann's syndrome (lesion of dominant parietal): ○ Alexia: in ability to read ○ Acalculia ○ Finger agnosia ○ Right-left disorientation.
Temporal Lobe	• Homonymous **superior quadrantanopia** • Prosopagnosia (difficulty recognising faces)	• Wernike's (recep**T**ive) aphasia • Memory impairment • Auditory agnosia
Occipital Lobe	• Cortical blindness (blindness due to damage to visual cortex, may present as Anton syndrome: there is blindness but patient is unaware or denies blindness) • **Homonymous hemianopia**	• Visual agnosia (seeing but not percieving objects - it is different to neglect since in agnosia the objects are seen and followed but cannot be named)

Dorsal column dysfunction: (joint position and light touch)
Spinothalamic dysfunction: (pinprick and temperature)
Thalamic and frontal lobe infarcts do not cause visual field defects.

DRIVING RULES (DVLA): Neurological aspect specific rules:

- First seizure: 6 months off driving (if the licence holder has undergone assessment by an appropriate specialist and no relevant abnormality has been identified on investigation, for example EEG and brain scan where indicate). For patients with established epilepsy they must be fit free for 12 months before being able to drive.
- Stroke or TIA: 1 month off driving
- Multiple TIAs over short period of times: 3 months off driving
- Craniotomy e.g. For meningioma: 1 year off driving (With benign tumors and if there is no seizure history, licence can be reconsidered in 6 months if remains seizure free)
- Pituitary tumour: craniotomy: 6 months; trans-sphenoidal surgery 'can drive when there is no debarring residual impairment likely to affect safe driving'
- Narcolepsy/cataplexy: cease driving on diagnosis, can restart once 'satisfactory control of symptoms'

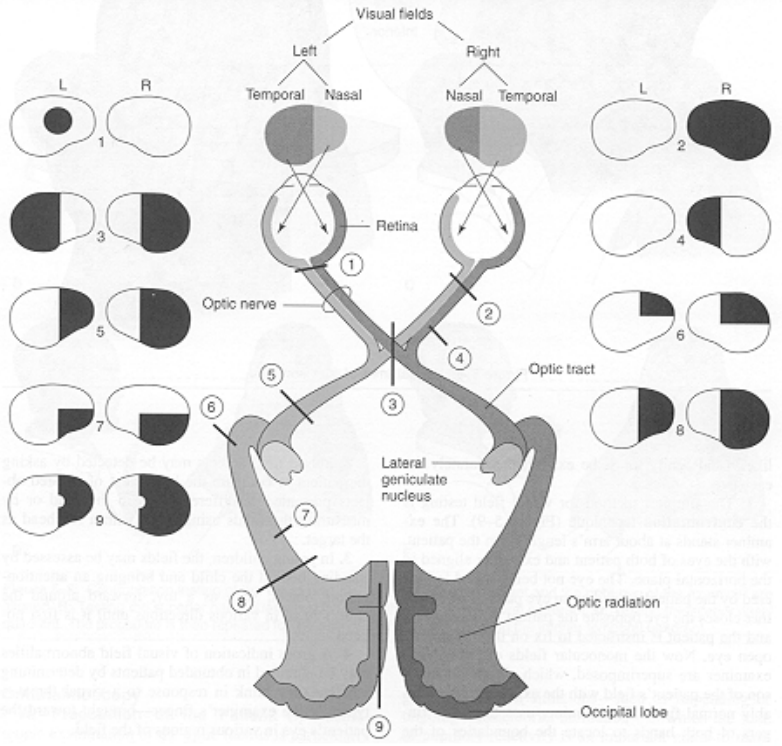
Cataplexy describes the loss of muscular tone caused by strong emotion (e.g. laughter, being frightened). Around two-thirds of patients with narcolepsy have cataplexy

Syncope

- Simple faint: no restriction
- Unexplained, low risk of recurrence: 4 weeks off
- Explained and treated: 4 weeks off
- Unexplained: 6 months off

Visual Field Defects:

- Rt homonymous hemianopia means visual field defect to the Rt, i.e. lesion of Lt optic tract (5)
- Homonymous quadrantanopias: PITS (Parietal-Inferior, Temporal-Superior) (7,6)



Homonymous Hemianopia

- Incongruous defects = optic tract lesion
- Congruous defects (defect is approximately the same in each eye) : optic radiation lesion or occipital cortex
- Macula sparing: lesion of occipital cortex (9)

Left homonymous hemianopia

Homonymous Quadrantanopias

- Superior: lesion of temporal lobe
- Inferior: lesion of parietal lobe
- Mnemonic = PITS (Parietal-Inferior, Temporal-Superior)

Bitemporal Hemianopia

- Lesion of optic chiasm
- Upper quadrant defect > lower quadrant defect = inferior chiasmal compression, commonly a pituitary tumour

Lower quadrant defect > upper quadrant defect = superior chiasmal compression, commonly a craniopharyngioma

Nystagmus: is defined as involuntary oscillations of the eyes. This may be pendular when the oscillations are equal in rate and amplitude, or jerking when there are quick and slow phases. (The quicker phase is used to define the direction.)

Causes:

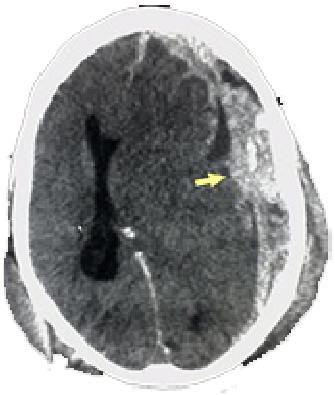
- Visual disturbances
- Lesions of the labyrinth
- The central vestibular connections
- Brain stem or cerebellar lesions.

Types:

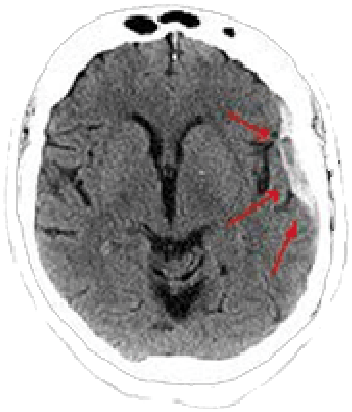
- Nystagmus which changes with the direction of gaze → involvement of vestibular nuclei.
- Pendular: mostly due to loss of macular vision, but could be in diffuse brain stem lesions.
- Jerking regardless of the direction of gaze → labyrinthine or cerebellar lesion.
- Jerking on lateral gaze, and fast in the direction of gaze → brain stem or cerebellum lesion.
- Nystagmus confined to one eye → nerve or muscle lesion, or medial longitudinal bundle lesion.
- Nystagmus restricted to the abducting eye on lateral gaze (ataxic nystagmus) is due to a lesion of the medial longitudinal bundle between the pons and mid-brain as in multiple sclerosis (MS).
- Wernicke's or thiamine deficiency is a rare cause of downbeat nystagmus

Medial Longitudinal Bundle → coordinates lateral rectus of one side with medial rectus of the other

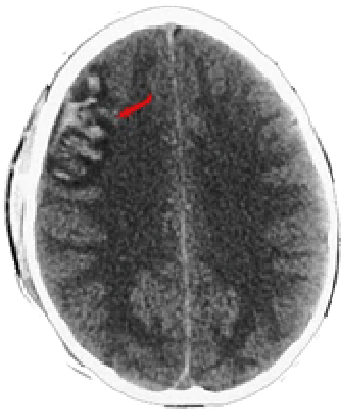
Upbeat nystagmus	Cerebellar vermis lesions
Downbeat nystagmus - foramen magnum lesions	Arnold-Chiari malformation

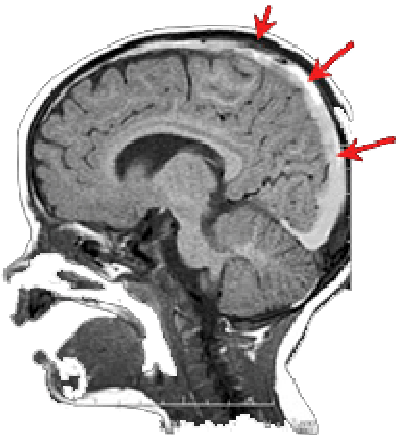


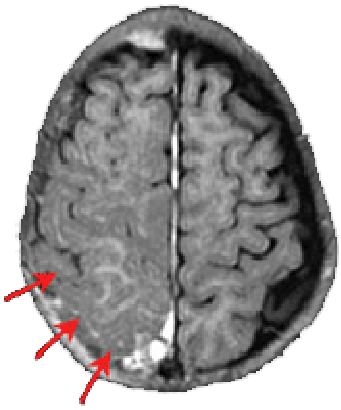
Subdural Hemorrhage



Subdural Hematoma







Subarachnoid Hemorrhage

Subdural Hemorrhage

The combination of falls, alcohol excess, fluctuating episodes of confusion and focal neurology points towards a diagnosis of subdural hemorrhage. The phrase 'fluctuating conscious level' is common in questions and should always bring to mind subdural hemorrhage

Basics

- Most commonly secondary to trauma e.g. Old person/alcohol falling over
- Initial injury may be minor and is often forgotten
- Caused by bleeding from damaged bridging veins between cortex and venous sinuses

Features

- Headache
- Classically fluctuating conscious level
- Raised ICP

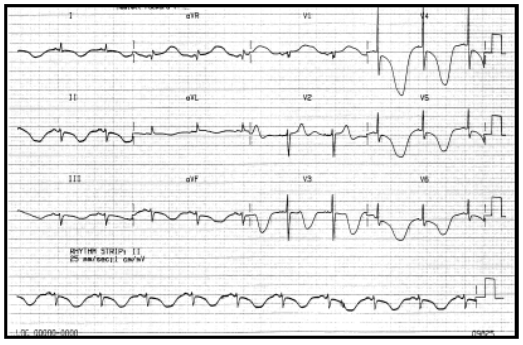
Treatment

- Needs neurosurgical review
- Burr hole →

Subarachnoid Hemorrhage:

Causes

- 85% are due to rupture of berry aneurysms (conditions associated with berry aneurysms include adult polycystic kidney disease, Ehlers-Danlos syndrome and coarctation of the aorta).
- AV malformations.
- Trauma.
- Tumours



Investigations

- CT: negative in 5%.
- LP: done after 12 Hrs (allowing time for xanthochromia to develop) If the CSF examination did not reveal xanthochromia, or there was still a high level of clinical suspicion, then cerebral angiography would be the next step

Complications

- Rebleeding (in 30%)
- Obstructive hydrocephalus (due to blood in ventricles)
- Vasospasm leading to cerebral ischemia

Intracranial hemorrhage can cause changes in the ECG which are typically deep symmetrical T-wave inversion and prolonged QT interval

Management

- Neurosurgical opinion: no clear evidence over early surgical intervention against delayed intervention
- Nimodipine (e.g. 60mg / 4 hrly, if BP allows) has been shown to ↓ the severity of neurological deficits but doesn't ↓ rebleeding*

*the way nimodipine works in subarachnoid hemorrhage is not fully understood. It has been previously postulated that it ↓ cerebral vasospasm (hence maintaining cerebral perfusion) but this has not been demonstrated in studies

Traumatic brain injury:

Extradural hematoma	Bleeding into the space between the dura mater and the skull. Often results from acceleration-deceleration trauma or a blow to the side of the head. The majority of epidural Hematomas occur in the temporal region where skull fractures cause a rupture of the middle meningeal artery. Features • Features of raised intracranial pressure • Some patients may exhibit a lucid interval
Subdural hematoma	Bleeding into the outermost meningeal layer. Most commonly occur around the frontal and parietal lobes. Risk factors include old age, alcoholism and anticoagulation. Slower onset of symptoms than a epidural Hematoma.
Subarachnoid hemorrhage	Usually occurs spontaneously in the context of a ruptured cerebral aneurysm but may be seen in association with other injuries when a patient has sustained a traumatic brain injury

Intracranial Venous Thrombosis

- Can cause cerebral infarction, much less common than arterial causes
- 50% of patients have isolated sagittal sinus thromboses - the remainder have coexistent lateral sinus thromboses and cavernous sinus thromboses

Features

- Headache (may be sudden onset)
- Nausea & vomiting
- Papilledema

Sagittal sinus thrombosis

- May present with seizures and hemiplegia
- Parasagittal biparietal or bifrontal hemorrhagic infarctions are sometimes seen

Cavernous sinus thrombosis

- Other causes of cavernous sinus syndrome: local infection (e.g. Sinusitis), neoplasia, trauma
- Ophthalmoplegia due to IIIrd, IVth and VIth nerve damage
- Trigeminal nerve involvement may lead to hyperaesthesia of upper face and eye pain
- Central retinal vein thrombosis
- Swollen eyelids

Lateral sinus thrombosis

- VIth and VIIth cranial nerve palsies

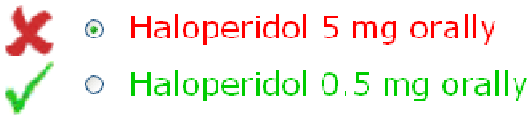
Acute Confusional State is also known as delirium or acute organic brain syndrome. It affects up to 30% of elderly patients admitted to hospital

Features - wide variety of presentations

- Memory disturbances (loss of short term > long term)
- May be very agitated or withdrawn
- Disorientation
- Mood change
- Visual hallucinations
- Disturbed sleep cycle
- Poor attention

Management

- Treatment of underlying cause
- Modification of environment
- **Haloperidol 0.5 mg** as 1st line then lorazepam



Wernicke Encephalopathy is a syndrome caused by lesions in the medial thalamic nuclei, mammillary bodies, periaqueductal and periventricular brainstem nuclei, and superior cerebellar vermis, often resulting from inadequate intake or absorption of thiamine (Vitamin B1), especially in conjunction with carbohydrate ingestion. Its most common correlate is prolonged alcohol consumption resulting in thiamine deficiency. Alcoholics are therefore particularly at risk, but it may also occur with thiamine deficiency states arising from other causes, particularly in patients with such gastric disorders as carcinoma, chronic gastritis, and repetitive vomiting, particularly after bariatric surgery.

In Wernicke's encephalopathy petechial hemorrhages occur in a variety of structures in the brain including the mamillary bodies and ventricle walls

Inability to acquire new memories and confabulation suggests the development of Korsakoff's syndrome

Features

- Nystagmus
- Ophthalmoplegia
- Ataxia
- Confusion, altered GCS
- Peripheral sensory neuropathy
- Impairment of short-term memory

Investigations

- ↓ Red cell transketolase
- MRI

Treatment is with urgent replacement of thiamine

Marchiafava Bignami syndrome: Corpus callosum degeneration from chronic alcohol excess

Urinary incontinence + gait abnormality + dementia = normal pressure hydrocephalus

Normal Pressure Hydrocephalus is a reversible cause of dementia seen in elderly patients. It is thought to be secondary to ↓ CSF absorption at the arachnoid villi. These changes may be secondary to head injury, subarachnoid hemorrhage or meningitis

A classical triad of features is seen

- Urinary incontinence
- Dementia and bradyphrenia (slowness of thought)
- Gait abnormality (may be similar to parkinson's disease)

Imaging

- Hydrocephalus with an enlarged fourth ventricle

Management

- Ventriculoperitoneal shunting

Idiopathic Intracranial Hypertension (also known as pseudotumour cerebri and formerly benign intracranial hypertension) is a condition classically seen in young, overweight ♀.

Obese, young ♀ with headaches / blurred vision think idiopathic intracranial hypertension

Features

- Headache
- Blurred vision
- Papilledema (usually present)
- Enlarged blind spot
- Sixth nerve palsy may be present

Risk factors

- Obesity
- ♀ sex
- Pregnancy
- Drugs (in this case it is not idiopathic): oral contraceptive pill, steroids, tetracycline, vitamin A

Investigations:

1. CT Scan
2. LP
3. Cerebral MRI with MR Venography

Management

- Weight loss
- Diuretics e.g. Acetazolamide
- Corticosteroids can be given
- Repeated lumbar puncture
- Surgery: optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve. A lumboperitoneal or ventriculoperitoneal shunt may also be performed to ↓ intracranial pressure

TIA: NICE issued updated guidelines relating to stroke and transient ischemic attack (TIA) in 2008. They advocated the use of the ABCD2 prognostic score for risk stratifying patients who've had a suspected TIA:

ABCD2 score of ≥4:

- Aspirin (300 mg daily) started immediately
- Specialist assessment and investigation within 24 hours of onset of symptoms
- Measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors

ABCD2 risk score ≤ 3:

- Specialist assessment within 1 week of symptom onset, including decision on brain imaging
- If vascular territory or pathology is uncertain, refer for brain imaging

	Criteria	Points
A	**A**ge ≥ 60 years	1
B	**B**lood pressure ≥ 140/90 mmHg	1
C	**C**linical features - Unilateral weakness - Speech disturbance, no weakness	 2 1
D	**D**uration of symptoms - > 60 minutes - 10-59 minutes	 2 1
D	Patient has diabetes	1
	Total	7

Recommendations from NICE (December 2010) include:

- ASA + Dipyridamole MR is still recommended as first choice for people who have had a TIA, but now there is no recommended limit on the duration of treatment. Clopidogrel is not recommended
- MR dipyridamole monotherapy is recommended after TIA only if ASA is contraindicated or not tolerated, again with no limit on duration of treatment.

People with crescendo TIAs (≥2 episodes in a week) should be treated as being at high risk of stroke, even though they may have an ABCD2 score of 3 or below.

Stroke: RCP Guidleines 2004 – NICE Guidelines 2010

Selected points relating to the management of acute stroke include:

- Blood **glucose, hydration, oxygen** saturation and **temperature** should be maintained within normal limits
- **BLOOD PRESSURE SHOULD NOT BE LOWERED** in the acute phase unless there are complications e.g. Hypertensive encephalopathy (the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this)
- ASA 300mg orally or rectally should be given as soon as possible if a hemorrhagic stroke has been excluded
- With regards to AF, the RCP state: 'anticoagulants should not be started until brain imaging has excluded hemorrhage, and usually after 14 days from the onset of an ischemic stroke'
- If the cholesterol is > 3.5 mmol/l patients should be commenced on a statin

Thrombolysis should only be given if:

- It is administered within 3 hours (SIGN recommend a window of 4.5 hours) of onset of stroke symptoms (unless as part of a clinical trial)
- Hemorrhage has been definitively excluded (i.e. Imaging has been performed)
- If patient is awaked with stroke, do not thrombolyse (even if reached in < 3 hours), exact time of stroke is unknown

Alteplase is currently recommended by NICE

NICE guidelines (**December 2010**): prevention of further occlusive vascular event (OVE) – (This guidlenes are not applicable to patient with risk of stroke due to AF, post coronary revascularization or carotid atery procedure)

- Clopidogrel is now recommended by NICE ahead of combination use of ASA + dipyridamole MR in people who have had:
  - Ischemic Stroke
  - Peripheral arterial disease
  - Multivascular disease
  - MI only if ASA is not tolerated or contraindicated
- Dipyridamole MR + ASA is recommended as an option to prevent (OVE) in paients with Hx of:
  - TIA
  - Ischemic stroke only if Clopidogrel is contraindicated
- Dipyridamole MR alone is recommended as an option to prevent (OVE) in paients with Hx of:
  - TIA only if ASA is contraindicated
  - Ischemic stroke only if Clopidogrel and ASA are contraindicated

With regards to carotid artery endarterectomy:

- Recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- Should only be considered if carotid stenosis > 70% according ECST* criteria or > 50% according to NASCET** criteria

*European Carotid Surgery Trialists' Collaborative Group
**North American Symptomatic Carotid Endarterectomy Trial

Secondary Prevention

1. Clopidogrel
2. Dipyridamole MR + ASA
3. Dipyridamole MR

Dipyridamole is not to be used in acute phase

Stroke by Anatomy:

Cerebral Arteries	Anterior	Middle	Posterior
	• Contralateral hemiparesis and sensory loss, lower extremity > upper • Disconnection syndrome (akinetic mute patient)	• Contralateral hemiparesis and sensory loss, upper extremity > lower • Contralateral hemianopia • Aphasia (Wernicke's) • Gaze abnormalities	• Contralateral hemianopia with macular sparing • Disconnection syndrome

Lacunar

- Present with either isolated hemiparesis, hemisensory loss or hemiparesis with limb ataxia

Lateral medulla (posterior inferior cerebellar artery- PICA)

- Ipsilateral: ataxia, nystagmus, dysphagia, facial numbness, cranial nerve palsy
- Contralateral: limb sensory loss

Pontine

- VI nerve: horizontal gaze palsy
- VII nerve
- Contralateral hemiparesis

Basilar Artery CVA is typically associated with a poor prognosis

- Most of patients present with nausea, vertigo and vomiting
- Some present with motor deficits, dysarthria and speech involvement or headaches
- May present with visual disturbances. This includes abducens nerve palsy, conjugate gaze palsy, internuclear ophthalmoplegia and ocular bobbing

- Locked-In Syndrome: patient is awake but is unable to respond in anyway except by vertical gaze and blinking (lesion is in ventral pons)
- 70% of patients presenting with basilar artery territory stroke are hypertensive.
- Management includes vigorous control of hypertension and antiplatelet agents.

Oxfordshire Community Stroke Scale:

- TACS (total anterior circulatory stroke): combination of the 3 elements
    - Higher cerebral dysfunction
    - Contralateral sensory/motor deficit
    - Visual field defect.
- PACS (partial anterior circulatory stroke): 2 of the 3 elements above, or new higher cerebral dysfunction.
- LACS (lacunar stroke):
    - Pure motor or pure sensory syndrome or
    - Ataxic hemiparesis or
    - Dysarthria or
    - Clumsy-hand syndrome.
- POCS (posterior circulation syndrome):
    - Bilateral motor/sensory deficit or
    - Disorder of conjugate eye movement, or
    - Solitary visual field defect, or
    - Cerebellar dysfunction, or
    - Crossed cranial nerve and sensory/motor signs.

Lateral Medullary Syndrome: also known as Wallenberg's syndrome, occurs following occlusion of the posterior inferior cerebellar artery, resulting in sensory and sympathetic disturbances

Cerebellar features

- Ataxia
- Nystagmus

Brainstem features

- Ipsilateral: dysphagia, facial numbness, cranial nerve palsy e.g. Horner's
- Contralateral: limb sensory loss (pyramidal tract signs)

Pituitary Apoplexy: sudden enlargement of pituitary tumour secondary to hemorrhage or infarction

Features

- Sudden onset headache similar to that seen in subarachnoid hemorrhage
- Vomiting
- Neck stiffness
- Visual field defects: classically bitemporal superior quadrantic defect
- Extraocular nerve palsies
- Features of pituitary insufficiency e.g. Hypotension secondary to hypoadrenalism
- Electrolytes disturbance.

Management: IV Hydrocortisone should be given to prevent adisonian crisis

Brown-Séquard syndrome: is a loss of sensation and motor function (paralysis and ataxia) that is caused by the lateral hemisection of the spinal cord.

Features:

- Ipsilateral loss of fine touch, vibration and proprioception
- Ipsilateral hyper-reflexia and extensor plantar reflex
- Contralateral loss of pain and temperature sensation occurs affecting the side.
- Segmental anaesthesia at the level of the lesion
- Complete syndrome picture is rare and many patients may only exhibit some features.
- Trauma is a common cause; demyelination due to multiple sclerosis is another common cause but any lateral cord lesion (ischaemia, hemorrhage, granuloma, tumour etc) may give this picture.

Syringomyelia is a developmental, slowly enlarging cavitaryexpansion of the cervical cord that produce progressive myelopathy. Symptoms begin insidiously in adolescence or early adulthood, progress irregularly, and may undergo spontaneous arrest for several years; most patients acquire a cervical-thoracic scoliosis.

Syringomyelia - spinothalamic sensory loss (pain and temperature)

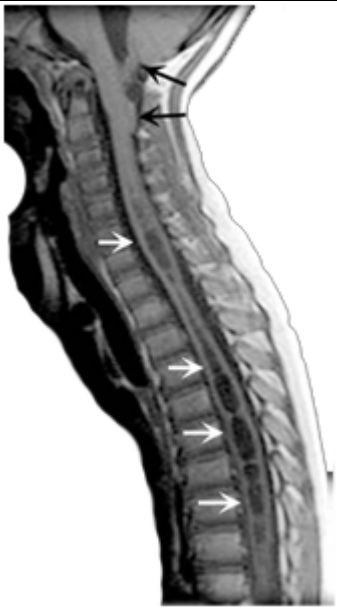
- Development of cavity (syrinx) within the spinal cord
- If extends into medulla then termed syringobulbia
- Strongly associated (>50%) with the arnold-chiari malformation

Features

- Maybe asymmetrical initially
- Slowly progressives, possibly over years
- Motor: wasting and weakness of arms
- Sensory: spinothalamic sensory loss (pain and temperature)
- Loss of reflexes, bilateral upgoing plantars
- Also seen: horner's syndrome

Localization of the lesion (for Part II):

- At syrinx (there is anterior horn cell involvement) → lower motor neuron pattern of weakness.
- At central decussating fibres (spinothalamic tract) → dissociated sensory loss with late development of neuropathic arthropathy.
- At corticospinal tracts below the level of the syrinx results in spastic paraparesis.



MRI of a syringomyelia associated with a Chiari malformation. Sagittal T1-weighted image through the cervical and upper thoracic spine demonstrates descent of the cerebellar tonsils and vermis below the level of the foramen magnum (*black arrows*). Within the substance of the cervical and thoracic spinal cord, a CSF collection dilates the central canal (*white arrows*).

MRI is the investigation of choice

Myelography used to confirm the diagnosis but was associated with more deterioration

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Transverse Myelitis: is an inflammatory lesion that can affect the cord. Constitutional symptoms such as headache and fever are common as is pain. Signs are indistinguishable from those caused by cord compression and again all sensory aspects are equally affected with no sparing of proprioception.

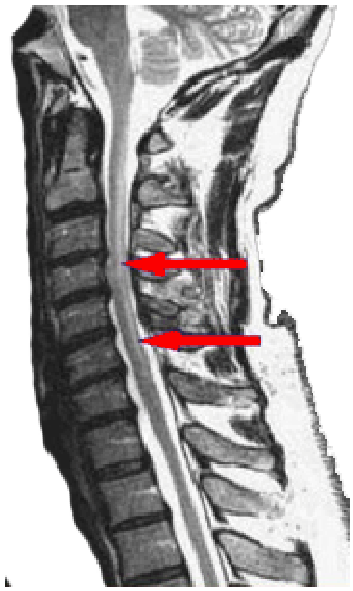
Subclavian Steal Syndrome: is associated with retrograde flow in the vertebral artery due to proximal subclavian artery stenosis. Neurological symptoms are precipitated by vigorous exercise with the arm above the head, such as painting a wall.

- Diagnosis is often confused with transient ischemic attacks or epilepsy.
- Duplex ultrasound and MRA are the investigations of choice.
- Endarterectomy and stenting are common surgical methods involved in relieving symptoms associated with this condition.

Subacute Combined Degeneration of Spinal Cord, also known as Lichtheim's disease, refers to degeneration of the posterior and lateral columns of the spinal cord as a result of vitamin B_{12} deficiency (most common), vitamin E deficiency or Friedrich's ataxia. It is usually associated with pernicious anemia.

Features:

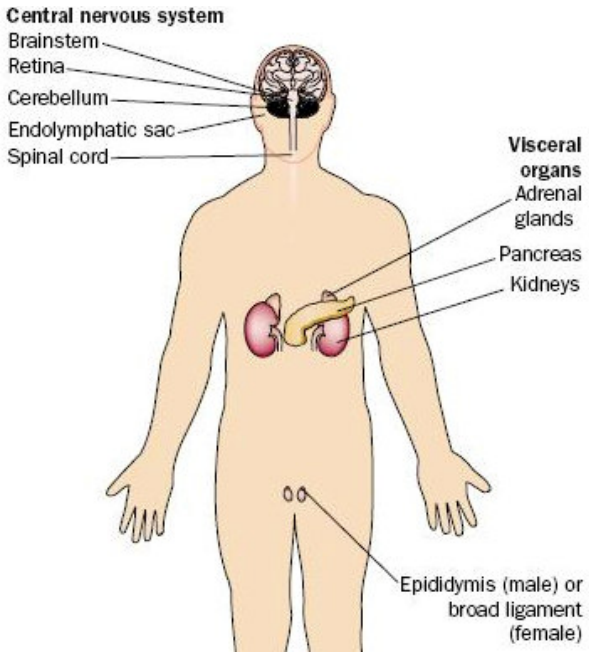
- Patchy losses of myelin in the dorsal and lateral columns.
- Present with progressive weakness of legs, arms, trunk, tingling and numbness.
- Visual & Mental changes may also be present.
- Bilateral spastic paresis may develop and pressure, vibration and touch sense are diminished.
- Positive Babinski sign may be seen.
- Prolonged deficiency (> 3 months) of vitamin B_{12} leads to irreversible nervous system damage.
- If someone is deficient in vitamin B_{12} and folic acid, the vitamin B_{12} deficiency must be treated first to avoid precipitating subacute combined degeneration of the cord.
- Therapy with vitamin B_{12} results in partial to full recovery, depending on the duration and extent of neurodegeneration



Narcolepsy is a condition causing excessive daytime somnolence and an overwhelming desire to sleep. Symptoms include excessive daytime sleepiness (EDS), involuntary sleep episodes –microsleeps- cataplexy (70%), sleep paralysis hallucinations - hypnagogic (at the onset of sleep) and hypnopompic (on awakening).

Von Hippel-Lindau: Retinal and cerebellar hemangiomas are key features of Von Hippel-Lindau syndrome. Retinal hemangiomas are bilateral in 25% of patients and may lead to vitreous hemorrhage

Von Hippel-Lindau (VHL) syndrome is an **autosomal dominant** condition predisposing to neoplasia. It is due to an abnormality in the VHL gene located on **short arm of chromosome 3**



Features:

- Cerebellar hemangiomas (Can secret crythyropiotiene that causes secondary polycythemia)
- Retinal hemangioma: vitreous hemorrhage
- Renal cysts (premalignant)
- Pheochromocytoma
- Extra-renal cysts: epididymal, pancreatic, hepatic
- Endolymphatic sac tumours

Friedreich's Ataxia is the most common of the early-onset hereditary ataxias. It is an **autosomal recessive**, trinucleotide repeat disorder characterized by a GAA repeat in the X25 gene on chromosome 9 (frataxin). **Friedreich's ataxia is unusual amongst trinucleotide repeat disorders in not demonstrating the phenomenon of anticipation**. **The typical age of onset is 10-15 years old**

Neurological features

- Absent ankle jerks/extensor plantars
- Cerebellar ataxia
- Optic atrophy
- Spinocerebellar tract degeneration

Other features

- Hypertrophic obstructive cardiomyopathy (90%, most common cause of death)
- Diabetes mellitus (10-20%)
- High-arched palate

Tuberous Sclerosis (TS) is a genetic condition of **autosomal dominant** inheritance. Like neurofibromatosis, the majority of features seen in TS are neuro-cutaneous

Cigarettes and coffee with a rough stupid person with a butterfly on his nose while he is dancing

Cigarettes (ash) - coffee (café-au-lait) - stupid (intellectual and developmental) - dancing (eplipsy)

Cutaneous features

- Depigmented 'ash-leaf' spots which fluoresce under UV light
- Roughened patches of skin over lumbar spine (Shagreen patches)
- Adenoma sebaceum: butterfly distribution over nose
- Fibromata beneath nails (subungual fibromata)
- Café-au-lait spots may be seen

Neurological features

- Developmental delay
- Epilepsy (infantile spasms or partial)
- Intellectual impairment

Also

- Retinal hamartomas: dense white areas on retina (phakomata)
- Rhabdomyomas of the heart
- Gliomatous changes can occur in the brain lesions
- Polycystic kidneys, renal angiomyolipomata

NF1: chromosome 17 - as neurofibromatosis has 17 characters
NF2: chromosome 22 - all the 2's
Lisch nodules are seen in neurofibromatosis

Neurofibromatosis: both types are inherited in an **autosomal dominant** fashion. NF1 is also known as von Recklinghausen's syndrome. It is caused by a gene mutation on chromosome 17 which encodes neurofibromin and affects around 1 in 4,000. NF2 is caused by gene mutation on chromosome 22 and affects around 1 in 100,000

Features

NF1	NF2
Café-au-lait spots (= 6, 15 mm in diameter) **Axillary/groin freckles** **Peripheral neurofibromas** **Iris: Lisch nodules in > 90%** **Scoliosis**	Bilateral acoustic neuromas

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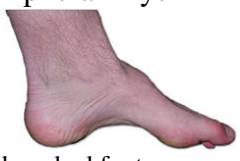
Hereditary Sensorimotor Neuropathy (HSMN) is a relatively new term which encompasses Charcot-Marie-Tooth disease (also known as peroneal muscular atrophy). Over 7 types have been characterized - however only 2 are common to clinical practice

- HSMN type I: primarily due to demyelinating pathology
- HSMN type II: primarily due to axonal pathology

HSMN type I

- **Autosomal dominant**
- Due to defect in PMP-22 gene (which codes for myelin) (PMP = Peripheral Myelin Protein)
- Features often start at puberty
- Motor symptoms predominate
- Distal muscle wasting, pes cavus, clawed toes
- Foot drop, leg weakness often first features
- Nerve Conduction Velocity is greatly ↓ <30m/second



High arched foot = pes cavus

Motor Neuron Disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It **rarely presents before 40 years** and various patterns of disease are recognized including **amyotrophic lateral sclerosis**, **primary lateral sclerosis**, **progressive muscular atrophy** and **bulbar palsy**. In some patients however, there is a combination of clinical patterns

Amyotrophic lateral sclerosis (50% of patients)

- Typically LMN signs in arms and UMN signs in legs
- In familial cases the gene responsible lies on chromosome 21 and codes for superoxide dismutase

Primary lateral sclerosis

- UMN signs only

Progressive muscular atrophy

- LMN signs only
- Affects distal muscles before proximal
- Carries best prognosis

Bulbar palsy

- Palsy of the tongue, muscles of chewing/swallowing and facial muscles due to loss of function of brainstem motor nuclei
- Carries worst prognosis

There are a number of clues which point towards a diagnosis of motor neuron disease:

- Fasciculation
- Absence of sensory signs/symptoms (vague sensory symptoms may occur early in the disease (e.g. Limb pain) but 'never' sensory signs)
- Lower motor neuron signs in arms and upper motor neuron signs in legs
- Wasting of the small hand muscles/tibialis anterior is common (tibialis anterior functions to stabilise the ankle as the foot hits the ground during the contact phase of walking [eccentric contraction] and acts later to pull the foot clear of the ground during the swing phase [concentric contraction]. It also functions to 'lock' the ankle, as in toe-kicking a ball, when held in an isometric contraction)

Other features

- Doesn't affect external ocular muscles
- No cerebellar signs
- Abdominal reflexes are usually preserved and sphincter dysfunction if present is a late feature.

The diagnosis of motor neuron disease is clinical, but nerve conduction studies will show normal motor conduction and can help exclude a neuropathy. Electromyography shows a ↓ number of action potentials with ↑ amplitude. MRI is usually performed to exclude the differential diagnosis of cervical cord compression and myelopathy

Management:
Riluzole

- Anti-glutamate drug
- **Used mainly in amyotrophic lateral sclerosis**
- Prolongs life by about 3 months
- Expensive

Respiratory care

- Non-invasive ventilation (usually BiPAP) is used at night
- Studies have shown a survival benefit of around 7 months

Prognosis

- Poor: 50% of patients die within 3 years

Lesions producing both upper motor and lower neuron signs

UMN (extensor plantars) and LMN (absent ankle jerk) signs

Causes

- Subacute combined degeneration of the cord
- Motor neuron disease
- Friedreich's ataxia
- Syringomyelia
- Syringobulbia
- Taboparesis (syphilis)
- Conus medullaris lesion

TABLE 348-7 Features That Distinguish Generalized Tonic-Clonic Seizure from Syncope

Features	Seizure	Syncope
Immediate precipitating factors	Usually none	Emotional stress, Valsalva, orthostatic hypotension, cardiac etiologies
Premonitory symptoms	None or aura (e.g., odd odor)	Tiredness, nausea, diaphoresis, tunneling of vision
Posture at onset	Variable	Usually erect
Transition to unconsciousness	Often immediate	Gradual over seconds[a]
Duration of unconsciousness	Minutes	Seconds
Duration of tonic or clonic movements	30–60 s	Never more than 15 s
Facial appearance during event	Cyanosis, frothing at mouth	Pallor
Disorientation and sleepiness after event	Many minutes to hours	<5 min
Aching of muscles after event	Often	Sometimes
Biting of tongue	Sometimes	Rarely
Incontinence	Sometimes	Sometimes
Headache	Sometimes	Rarely

[a] May be sudden with certain cardiac arrhythmias.

Epilepsy is more likely to occur in young children or people over the age of 65 years; however it can occur at any time. Epilepsy is usually controlled, but not cured, with medication, although surgery may be considered in difficult cases. Over 30% of people with epilepsy do not have seizure control even with the best available medications. Not all epilepsy syndromes are lifelong – some forms are confined to particular stages of childhood. Epilepsy should not be understood as a single disorder, but rather as syndromic with vastly divergent symptoms but all involving episodic abnormal electrical activity in the brain.

Basics

- Two main categories: generalised and partial seizures
- Partial seizures may progress to general seizures
- Other types: myoclonic, atypical absence, atonic and tonic seizures are usually seen in childhood

Generalised - no focal features, consciousness lost immediately

- Grand mal (tonic-clonic)
- Petit mal (absence seizures)
- Partial seizures progressing to generalised seizures

Partial - focal features depending on location

- Simple (no disturbance of consciousness or awareness)
- Complex (consciousness is disturbed)
- Temporal lobe → aura, déjà vu, jamais vu; motor → jacksonian

Myoclonus

- Occur in a variety of conditions

Complex partial seizures can take the form of automatisms, such as chewing and swallowing, repeatedly scratching the head or searching for an object. Some people may even undress. They can occur as a result of seizure activity in any part of the brain but most commonly arise in the temporal lobes.

Traeatment:

Monotherapy should be attempted before combination therapy is started. **Caution should be exercised when combining sodium valproate and lamotrigine as serious skin rashes such as Steven-Johnson's syndrome** may be provoked.

Most neurologists now start antiepileptics following a second epileptic seizure. NICE guidelines suggest starting antiepileptics after the first seizure if any of the following are present:

- The patient has a neurological deficit
- Brain imaging shows a structural abnormality
- The EEG shows unequivocal epileptic activity
- The patient or their family or carers consider the risk of having a further seizure unacceptable

Na valproate is 1st line for generalised seizures – Carbamazepine used for partial seizures

Tonic-Clonic Seizures

- Sodium valproate
- Second line: lamotrigine (Lamictal®), carbamazepine (Tegretol®)

Absence Seizures* (Petit Mal)

- Sodium valproate or ethosuximide (in isolated absences)
- Sodium valproate particularly effective if co-existent tonic-clonic seizures in primary generalised epilepsy

Myoclonic Seizures

- Sodium valproate
- Second line: clonazepam, lamotrigine

Partial Seizures

- Carbamazepine (Tegretol®)
- Second line: lamotrigine**, sodium valproate
- Gabapentin (Neurontin®, Gabarone®)

* Carbamazepine may actually exacerbate absence seizure
** The 2007 SANAD study indicated that lamotrigine may be a more suitable first-line drug for partial seizures although this has yet to work its way through to guidelines.

Vigabatrin – rarley used anti-epileptic

- 40% of patients develop **Visual field defects**, which may be irreversible
- Visual fields should be checked every 6 months

Absence Seizures (Petit Mal) are a form of generalised epilepsy that is mostly seen in children. The typical age of onset of 3-10 years old and girls are affected twice as commonly as boys

Features

- Absences last a few seconds and are associated with a quick recovery
- Seizures may be provoked by hyperventilation or stress
- The child is usually unaware of the seizure
- They may occur many times a day
- EEG: bilateral, symmetrical 3Hz (spike and wave) pattern

Management

- Sodium valproate and ethosuximide are first-line treatment
- Good prognosis - 90-95% become seizure free in adolescence

AED cessation can be considered if seizure free for > 2 years – Stop AEDs over 2-3 months

In a patient who has been seizure free for more than 2 years, the chance of recurrence in the next 2 years is 43% if they stop therapy compared with 10% if drugs are continued. Factors that have been shown to increase the risk of seizures include:

- Older age
- Use of multiple anticonvulsants
- History of myoclonic or tonic clonic seizure
- Previous abnormal imaging or EEG
- Seizure while on therapy.

The risks of uncontrolled **epilepsy during pregnancy** generally outweigh the risks of medication to the fetus. All women thinking about becoming pregnant should be advised to take folic acid 5mg/day well before pregnancy to minimise the risk of neural tube defects. Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication

Other points

- Aim for monotherapy
- There is no indication to monitor antiepileptic drug levels
- Sodium valproate: associated with neural tube defects
- Phenytoin (Epanutin®): associated with cleft palate
- Lamotrigine: studies to date suggest the rate of congenital malformations may be low. The dose of lamotrigine may need to be increased in pregnancy
- Carbamazepine: often considered the least teratogenic of the older antiepileptics

Breast feeding is generally considered safe for mothers taking antiepileptics with the possible exception of the barbiturates

It is advised that pregnant women taking phenytoin are given vitamin K in the last month of pregnancy to prevent clotting disorders in the newborn

Infantile Spasm (West syndrome):

- Occurs between 3-12 month of age, managed by Vegabatrin (S.E causes alopecia, ↓ visual acuity diplopia).
- West syndrome is the triad of infantile spasms, a pathognomonic EEG pattern (called hypsarrhythmia), and mental retardation - although the international definition requires only two out of these three elements.

Functional (Non-Epileptic) Seizures are common and occur in 10–20% of patients referred to specialist epilepsy clinics with intractable seizures. The history of the attacks is usually suggestive but is not diagnostic of their functional nature.

Non-epileptic attacks are broadly divided into:

- Hyperkinetic/thrashing attacks
- Akinetic/motionless attacks.

There are no clinical signs which never occur in epilepsy (although some are very rare) and no signs are unique to epilepsy (apart from ictal electroencephalography (EEG) abnormalities). The 'strangeness' of an attack should in itself not imply a diagnosis of non-epileptic attack.

Distinguish functional from epileptic seizures:

- Asynchronous limb movements
- Undulating motor activity
- Purposeful movements
- Rhythmic pelvic movements
- Side-to-side head shaking
- Biting the tip of the tongue (as opposed to the side)
- Ictal crying
- Vocalisation during the 'tonic–clonic' phase
- Closed eyelids, resistance to eyelid opening
- Lack of cyanosis and rapid post-ictal reorientation

Prolactin is often elevated 15–20 min after a tonic–clonic seizure and should be normal in non-epileptic attacks, but there are a number of problems: serum rises are seen in syncopal episodes; it may be normal, especially in partial epileptic seizures; and the test is often badly carried out in practice (too early or too late). It is therefore generally not recommended outside specialist centres. **Video telemetry is the gold standard investigation** for possible functional seizures.

Parkinson's Disease is a progressive neurodegenerative condition caused by degeneration of dopaminergic neurons in the substantia nigra, thus results in a classic triad of features: bradykinesia, asymetrical tremor and rigidity. The symptoms of Parkinson's disease are characteristically asymmetrical

Bradykinesia

- Poverty of movement also seen: mask-like face
- Difficulty in initiating movement

Tremor

- Most marked at rest, 3-5 Hz
- Typically 'pill-rolling'

Rigidity

- Lead pipe
- Cogwheel: due to superimposed tremor

Reversible Causes	*Irreversible/Degenerative Dementias*	*Psychiatric Disorders*
Examples	Examples	Depression
Hypothyroidism	Alzheimer's	Schizophrenia
Thiamine deficiency	Frontotemporal dementia	Conversion reaction
Vitamin B_{12} deficiency	Huntington's	
Normal-pressure hydrocephalus	Dementia with Lewy bodies	
Chronic infection	Multi-infarct	
Brain tumor	Leukoencephalopathies	
Drug intoxication	Parkinson's	

Additional Useful Information (*Harrison's Principles of Internal Medicine)*

Other characteristic features

- Flexed posture
- Short, shuffling steps
- Micrographia
- Drooling of saliva
- Psychiatric features: depression is the most common feature (affects about 40%); dementia, psychosis and sleep disturbances may also occur
- Impaired olfaction
- REM sleep behaviour disorder

Causes of Parkinsonism

- Parkinson's disease
- Drug-induced e.g. Antipsychotics, metoclopramide - see below
- Progressive supranuclear palsy
- Multiple system atrophy
- Wilson's disease
- Post-encephalitis
- Dementia pugilistica (secondary to chronic head trauma e.g. Boxing)
- Toxins: carbon monoxide, MPTP

Drug-induced Parkinsonism has slightly different features to Parkinson's disease:

- Motor symptoms are generally rapid onset and bilateral
- Rigidity and rest tremor are uncommon

Drugs causing Parkinsonism

- Phenothiazines: e.g. Chlorpromazine
- Butyrophenones: haloperidol, droperidol
- Metoclopramide

Domperidone does not cross the blood-brain barrier and therefore does not cause extra-pyramidal side-effects

Management:
Currently accepted practice in the management of patients with Parkinson's disease (PD) is to delay treatment until the onset of disabling symptoms and then to introduce a dopamine receptor agonist. If the patient is elderly, levodopa is sometimes used as initial treatment.

Dopamine receptor agonists (favored for patients > 75yrs old)

- E.g. Bromocriptine, Pramipexole, Ropinirole, Cabergoline, Apomorphine
- Ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide*) have been associated with pulmonary, retroperitoneal and cardiac fibrosis. The Committee on Safety of Medicines advice that an ESR, creatinine and CXR should be obtained prior to treatment and patients should be closely monitored
- Ropinirole is least associated with tissue fibrosis.
- Patients should be warned about the potential for dopamine receptor agonists to cause impulse control disorders and excessive daytime somnolence

Levodopa	Adverse effects of L-Dopa
• Usually combined with a decarboxylase inhibitor (e.g. Carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine • ↓ effectiveness with time (usually by 2 years) • Unwanted effects: dyskinesia, 'on-off' effect • Not used in neuroleptic induced parkinsonism • Favoed for patients < 75yrs	• Dyskinesia • 'On-off' effect • Postural hypotension • Cardiac arrhythmias • Nausea & vomiting • Psychosis • Reddish discolouration of urine upon standing

MAO-B (Monoamine Oxidase-B) inhibitors

- E.g. Selegiline
- Inhibits the breakdown of dopamine secreted by the dopaminergic neurons

Amantadine

- Mechanism is not fully understood, probably ↑ dopamine release and inhibits its uptake at dopaminergic synapses

COMT (Catechol-O-Methyl Transferase) inhibitors

- E.g. Entacapone
- COMT is an enzyme involved in the breakdown of dopamine, and hence may be used as an adjunct to levodopa therapy
- Used in established PD

Antimuscarinics

- Block cholinergic receptors
- Now used more to treat drug-induced parkinsonism rather than idiopathic Parkinson's disease
- Help tremor and rigidity
- E.g. procyclidine, benzotropine, trihexyphenidyl (benzhexol)

***pergolide was withdrawn from the US market in March 2007 due to concern regarding ↑ incidence of valvular dysfunction**

Multiple system atrophy: Shy-Drager syndrome is a type of multiple system atrophy

Features

- Parkinsonism
- Autonomic disturbance (atonic bladder, postural hypotension)
- Cerebellar signs

PSP: parkinsonism, impairment of vertical gaze

Impairment of vertical gaze is seen in progressive supranuclear palsy. Horizontal gaze impairment is sometimes seen later as the disease progresses, but would be atypical in a newly diagnosed patient.

Progressive Supranuclear Palsy is degenerative disease involving the gradual deterioration and death of selected areas of the brain. Both ♂ and ♀ are affected approximately equally and there is no racial, geographical or occupational predilection. Approximately 6 people per 100,000.

- AKA Steele-Richardson-Olszewski syndrome
- A 'Parkinson Plus' syndrome

Features

- Impairment of vertical gaze (down gaze worse than up gaze - patients may complain of difficultly reading or descending stairs)
- Parkinsonism
- Falls
- Slurring of speech
- Cognitive impairment

Management

- Poor response to L-dopa

Lewy Body Dementia is an increasingly recognised cause of dementia, accounting for up to 20% of cases. The characteristic pathological feature is cytoplasmic neuronal inclusions (Lewy bodies) in the substantia nigra, paralimbic and neocortical areas

The relationship between Parkinson's disease and Lewy body dementia is complicated, particularly as dementia is often seen in Parkinson's disease. Also, up to 40% of patients with Alzheimer's have Lewy bodies.

Neuroleptics should be avoided in Lewy body dementia as patients are extremely sensitive and may develop irreversible Parkinsonism. Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent

Features

- Progressive cognitive impairment
- Parkinsonism
- Visual hallucinations (other features such as delusions and non-visual hallucinations may also be seen)

Dementia is though to affect over 700,000 people in the UK and accounts for a large amount of health and social care spending. The most common cause of dementia in the UK is Alzheimer's disease followed by vascular and Lewy body dementia. These conditions may coexist.

Features

- Diagnosis can be difficult and is often delayed
- The mini-mental state examination is widely used. A score < 24 out of 30 suggests dementia

Management

- In primary care a blood screen is usually sent to exclude reversible causes (e.g. Hypothyroidism). **NICE recommends the following tests: FBC, U&E, LFTs, calcium, glucose, TFTs, vitamin B12 and folate levels**. Patients are now commonly referred on to old-age psychiatrists (sometimes working in 'memory clinics').
- In secondary care neuroimaging is performed* to exclude other reversible conditions (e.g. Subdural hematoma, normal pressure hydrocephalus) and help provide information on aetiology to guide prognosis and management

*in the 2006 NICE guidelines structural imaging was said to be essential for diagnosis

Frontotemporal Lobar Degeneration (Pick Disease):

- Progressive neurodegenerative disorder comprising of dementias.
- Insidious behavioral and cognitive symptoms: aggressiveness and inappropriate behavior, stereotyped behavior, apathy and depression. Speech and language abnormalities begin early and progress rapidly.
- Memory is less severely affected than in Alzheimer disease.
- Brain CT or MRI may show selective atrophy of the frontal and temporal lobes.
- Mini-Mental Score (MMSE): is often surprisingly high, and more formal neuropsychological testing may be required to establish the typical cognitive deficits
- 50% of cases have an affected family member.
- A subgroup of patients with frontotemporal dementia has symptoms and signs of motor neuron disease. This is evidenced by the lower motor neuron signs of impaired swallow, proximal limb weakness and fasciculation's indicating recent denervation.
- Treatment is supportive.

Essential tremor:

(previously called benign essential tremor) is an autosomal dominant condition which usually affects both upper limbs.

Essential tremor is an AD condition that is made worse when arms are outstretched, made better by alcohol and propranolol

Features

- Postural tremor: worse if arms outstretched (usually 6-8 Hz)
- Improved by alcohol and rest
- Most common cause of titubation (head tremor)

Management

- Propranolol is first-line
- Primidone (anticonvulsant) is sometimes used when propanolol is contraindicated

Creutzfeldt - Jakob disease (CJD): Basics & Features:

- Rapidly progressive, severe and invariably fatal (usually within few months)
- Dementia
- Cerebellar ataxia
- Defuse myoclonic jerks
- Other neurological abnormalities.

Myoclonus is typical and progressive, even during the later stage when the patient is stuporous or comatose.

Investigation:

- The EEG patern is characteristic (diffuse non specific slowing periodic sharp wave complexes-PSWCs of 1 – 2 Hz), but diagnosis relies on either espiecalized tests for prion protein in CSF or direct brain biopsy.
- Pulvinar Sign on cranial MRI > 90% pathological in vCJD (Not Sporadic)
- Prion protien in tonsils
- 14-3-3 protien in CSF

Sporadic CJD predominantly affects late mid-aged individuals with mean age of death in the late 60s. Memory impairment and cerebellar ataxia are common early features, subsequently, rapidly progressive dementia and myoclonus. The median duration of illness is 4 months and about 65% of caeses die within 6 months.

Alzheimer's Disease progressive degenerative disease of brain. Major cause of dementia in UK

Genetics

- Most cases are sporadic
- 5% are inherited as an autosomal dominant trait
- Mutations in the amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1) genes are thought to cause the inherited form
- Apoprotein E allele E4 - encodes a cholesterol transport protein

Pathological changes

- Macroscopic = widespread cerebral atrophy, particularly involving the cortex and hippocampus
- Microscopic = intraneuronal neurofibrillary tangles, neuronal plaques, deficiency of neurons
- Biochemical = deposition of type A-β-amyloid protein in cortex, deficit of Ach from damage to an ascending forebrain projection

Neurofibrillary tangles

- Paired helical filaments are partly made from a protein called tau
- In Alzheimer: tau proteins are excessively phosphorylated

Management

- NICE now recommend the three acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine) as options for managing mild to moderate Alzheimer's disease. Donepezil may cause bradycardia and atrioventricular node block.
- Memantine is reserved for patients with moderate - severe Alzheimer's.

Tau proteins are proteins that stabilize microtubules. They are abundant in neurons in the central nervous system and are less common elsewhere. When tau proteins are defective, and no longer stabilize microtubules properly, they can result in dementias, such as Alzheimer's disease.

Hemiballism occurs following damage to the **subthalamic nucleus**.

Features - Ballisic movements:

- Involuntary, sudden, jerking movements which occur contralateral to the side of the lesion
- Primarily affect the proximal limb musculature whilst the distal muscles may display more choreiform-like movements.
- Symptoms may decrease during sleeping.
- Etiology: stroke in elders, infection or inflammatory in young.
- Antidopaminergic agents (e.g. Haloperidol) are the mainstay of treatment. Tetrabenazine may be considered when long-term therapy is required.

Causes of Chorea:

• **Huntington's disease, Wilson's disease, ataxic telangiectasia** • **SLE, anti-phospholipid syndrome** • **Rheumatic fever: Sydenham's chorea** • **Drugs: oral contraceptive pill, L-dopa, antipsychotics**	• **Chorea gravidarum** • **Thyrotoxicosis** • **Polycythemia rubra vera** • **Carbon monoxide poisoning** • **Neuroacanthocytosis** • **Cerebrovascular disease**

Facial nerve

Supply - 'face, ear, taste, and tear'

- Face: muscles of facial expression
- Ear: nerve to stapedius
- Taste: supplies anterior two-thirds of tongue
- Tear: parasympathetic fibres to lacrimal glands, also salivary glands

Facial Palsy + convergent squint
↓
lesion is in Pons as VIth is encircled by VIIth

Causes of bilateral facial nerve palsy

- Sarcoidosis
- Guillain-Barre syndrome
- Polio, Lyme disease

Causes of unilateral facial nerve palsy - as above plus

Lower motor neuron	**Upper motor neuron**
• Bell's palsy • Ramsay-Hunt syndrome (due to herpes zoster) • Acoustic neuroma • Parotid tumours • HIV • Multiple Sclerosis • Diabetes Mellitus	• Stroke

LMN vs. UMN

- Upper motor neuron lesion 'spares' upper face i.e. Forehead
- Lower motor neuron lesion affects all facial muscles

Bell's palsy may be defined as an acute, unilateral, idiopathic, facial nerve paralysis. The aetiology is unknown although the role of the herpes simplex virus has been investigated previously.

Features

- Lower motor neuron facial nerve palsy - forehead affected*
- Patients may also notice post-auricular pain (may precede paralysis), altered taste, dry eyes

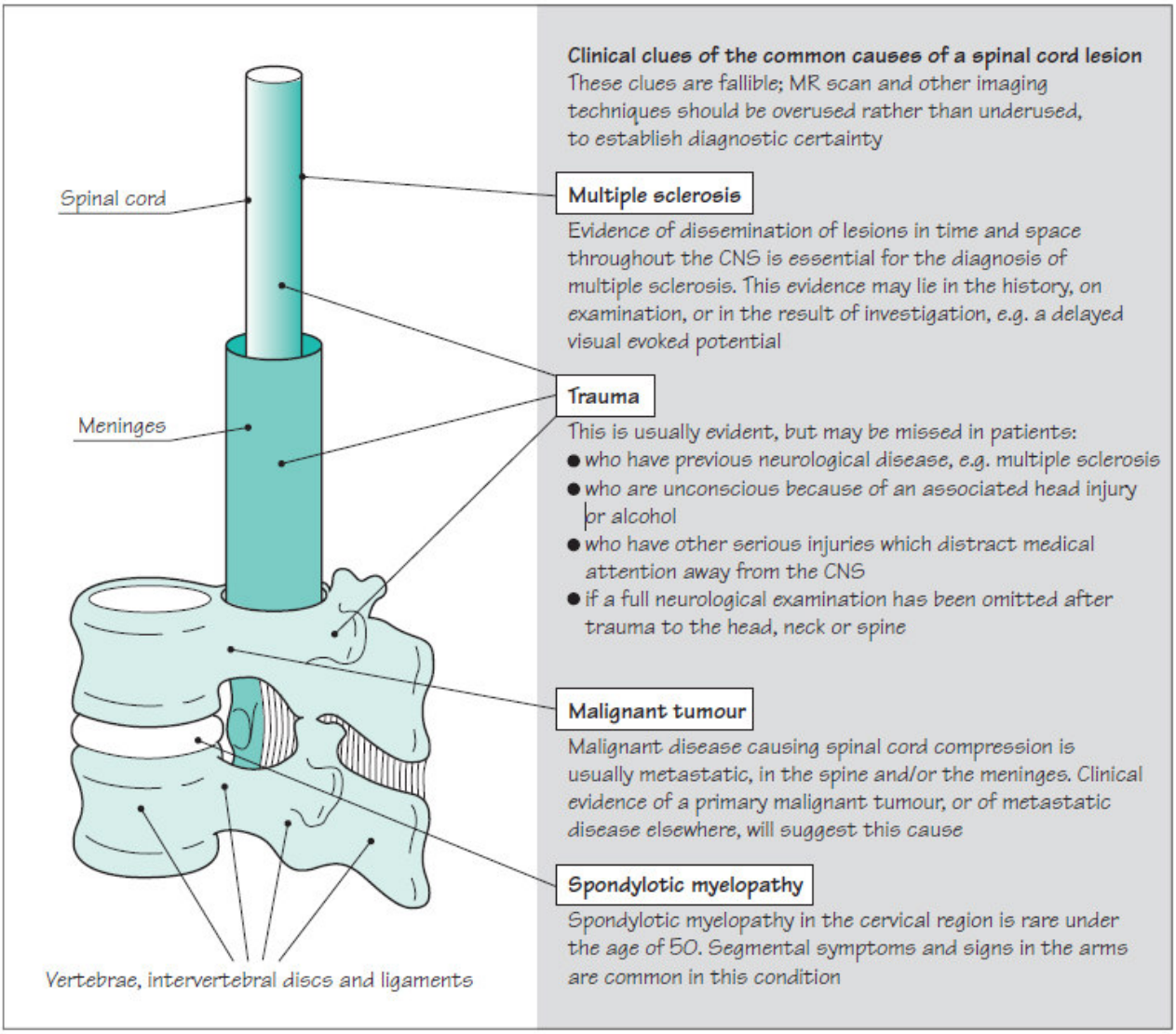
Management

- In the past a variety of treatment options have been proposed including no treatment, prednisolone only and a combination of aciclovir and prednisolone
- Following a National Institute for Health randomised controlled trial it is now recommended that prednisolone 25mg BD for 10 days should be prescribed for patients within 72 hours of onset of Bell's palsy. Adding in aciclovir gives no additional benefit
- Eye care is important - prescription of artificial tears and eye lubricants should be considered

Prognosis

- If untreated around 15% of patients have permanent moderate to severe weakness

*upper motor neuron lesion 'spares' upper face



Multiple Sclerosis: **(it is an UML)** also known as disseminated sclerosis or encephalomyelitis disseminate, is an autoimmune disease in which the body's immune response attacks a person's central nervous system (brain and spinal cord), leading to demyelination. Disease onset usually occurs in young adults, and it is more common in ♀.

Relapsing-remitting: Characterized by unpredictable relapses followed by periods of months to years of relative quiet (remission) with no new signs of disease activity. Deficits suffered during attacks may either resolve or leave sequelae. This describes the initial course of 85–90% of individuals with MS. When deficits always resolve between attacks, this is sometimes referred to as benign MS.

Secondary progressive: Describes those with initial relapsing-remitting MS, who then begin to have progressive neurologic decline between acute attacks without any definite periods of remission. Occasional relapses and minor remissions may appear. The median time between disease onset and conversion from relapsing-remitting to secondary progressive MS is 19 years.

Primary progressive: Describes the approximately 10–15% of individuals who never have remission after their initial MS symptoms. It is characterized by progression of disability from onset, with no, or only occasional and minor, remissions and improvements. The age of onset for the primary progressive subtype is later than other subtypes.

Progressive relapsing: Describes those individuals who, from onset, have a steady neurologic decline but also suffer clear superimposed attacks. This is the least common of all subtypes.

Non-standard behaviors: Have also been described. Sometimes referred to as borderline forms of MS, these include Devic's disease, Balo concentric sclerosis, Schilder's diffuse sclerosis and Marburg MS. MS also behaves differently in children. There is debate whether these are atypical variants of MS or different diseases

Features

Visual

- Optic neuritis: common presenting feature
- Optic atrophy
- Uhthoff's phenomenon: worsening of vision following rise in body temperature (hot bath)
- Internuclear ophthalmoplegia

Sensory

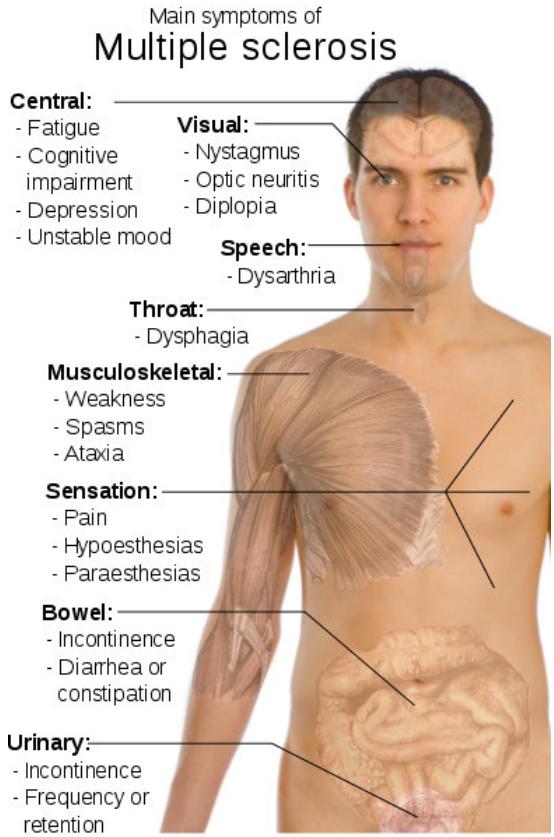
- Pins/needles
- Numbness
- Trigeminal neuralgia
- Lhermitte's syndrome: paraesthesiae in limbs on neck flexion

Motor

- Spastic weakness

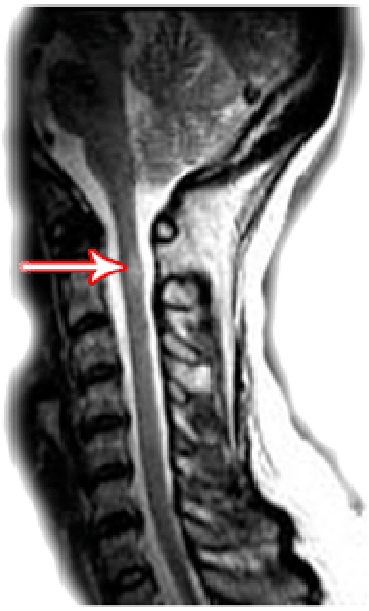
Cerebellar

- Ataxia, Tremor



Others

- Urinary incontinence
- Sexual dysfunction
- Intellectual deterioration



Good prognosis features

- ♀ sex
- Young age of onset
- Relapsing-remitting disease
- Sensory symptoms
- long interval between first two relapses

To remember prognostic features

- The typical patient carries a better prognosis than an atypical presentation

Diagnosis requires demonstration of lesions disseminated in time and space

MRI

- High signal T2 lesions
- Periventricular plaques

CSF

- Oligoclonal bands (and not in serum)
- ↑ intrathecal synthesis of IgG

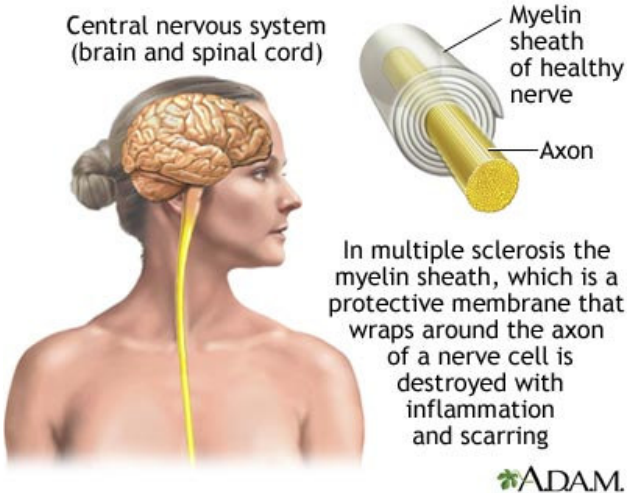
Visual evoked potentials

- Delayed, but well preserved wave form

Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses. There is no cure. High dose steroids (e.g. IV **methylprednisolone**) may be given for 3-5 days to shorten the length of an acute relapse. **Baclofen** is helpful in controlling spasticity. Hallucinations are occasionally seen on the withdrawal of baclofen

β-interferon has been shown to ↓ the relapse rate by up to 30%. Certain criteria have to be met before it is used:

- Relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
- Secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)
- ↓ number of relapses and MRI changes. However doesn't ↓ overall disability

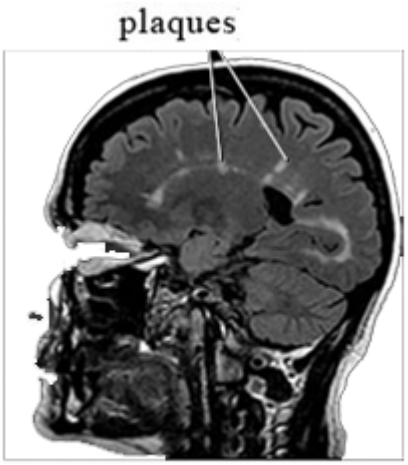


Other drugs used in the management of multiple sclerosis include:

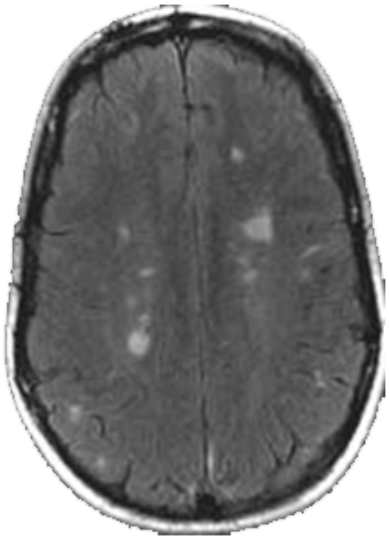
- Glatiramer acetate: immunomodulating drug
- Natalizumab: a recombinant monoclonal antibody that antagonises α4β1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium into parenchymal tissue

Symptom control

- Spasticity: baclofen and gabapentin are first-line. Other options include diazepam, dantrolene and tizanidine



Brain with damage (lesions or plaques) caused by MS



Plaques on MRI in MS

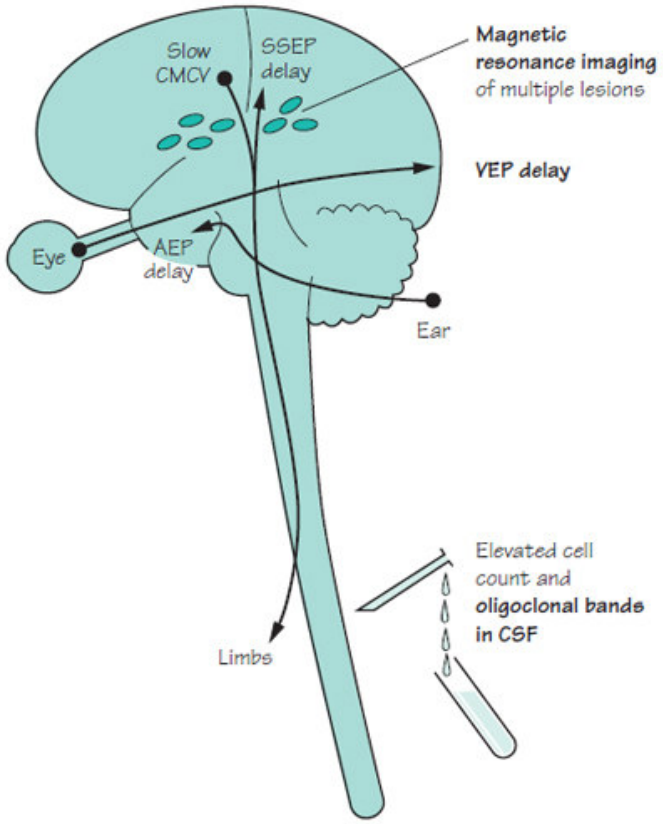


Diagram to show the abnormal investigations in patients with multiple sclerosis. None is specific. MR scanning is used. CSF abnormalities are found, especially the presence of oligoclonal bands in the CSF globulin. AEP, auditory evoked potential from ear to temporal cortex; CMCV, central motor conduction velocity from motor cortex to limbs; SSEP, somatosensory evoked potential from limbs to sensory cortex; VEP, visual evoked potential from eye to occipital cortex.

Miosis:

Ptosis + dilated pupil = third nerve palsy	Ptosis + constricted pupil = Horner's

Causes of miosis (small pupil)

- Horner's syndrome
- Argyll-Robertson pupil
- Senile miosis
- Pontine hemorrhage
- Congenital

Lt. Sided Horner Syndrome

Drugs causes

- Opiates
- Parasympathomimetics: pilocarpine
- Organophosphate toxicity

Holmes-Adie pupil is a benign condition most commonly seen in women. It is one of the differentials of a dilated pupil

Argyll-Robertson: small irregular pupils that do not react to light but react to accommodation.
Referred to as the "Whore's Eye" because of the association with tertiary syphilis and because of the convenient mnemonic that, like a prostitute, they "accommodate but do not react"

Causes: Multiple Sclerosis, Sarcoidoisis, DM

Horner's Syndrome:

Features:

- Miosis (small pupil)
- Ptosis
- Enophthalmos (sunken eye) in reality the appearance is due to a narrow palpebral aperture rather than true enophthalmos
- Anhydrosis (loss of sweating one side)

Distinguishing between causes

- Heterochromia (difference in iris color) is seen in congenital Horner's, like in the opposite figure, note the Lt Eye color.
- Anhydrosis: see below

Horner's syndrome - anhydrosis determines site of lesion:

- Head, arm, trunk = central lesion: stroke, syringomyelia
- Just face = pre-ganglionic lesion: Pancoast's, cervical rib
- Absent = post-ganglionic lesion: carotid artery

STC

Central lesions	Pre-ganglionic lesions	Post-ganglionic lesions
Anhydrosis of the face, arm and trunk	Anhydrosis of the face	No anhydrosis
Stroke **S**yringomyelia Multiple **S**clerosis Tumour Encephalitis	Pancoast's **T**umour **T**hyroidectomy **T**rauma Cervical rib	**C**arotid artery dissection **C**arotid aneurysm **C**avernous sinus thrombosis **C**luster headache

Ptosis	Causes of bilateral ptosis	Causes of unilateral ptosis (bilateral causes+)
	• **Myotonic dystrophy** • **Myasthenia gravis*** • **Syphilis** • **Congenital**	• **Third nerve palsy** • **Horner's**

*ptosis is much less common in Lambert-Eaton syndrome than myasthenia gravis

Painful third nerve palsy = posterior communicating artery aneurysm

Given a combination of a headache + 3rd nerve palsy it is important to exclude a PCA aneurysm

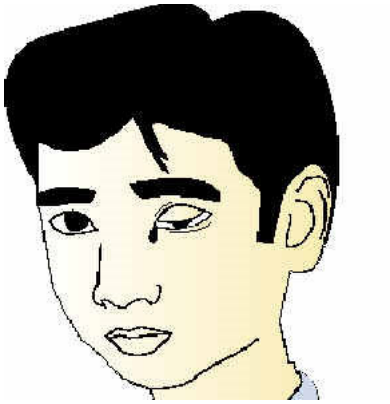
Third nerve palsy

Features

- Eye is deviated 'down and out'
- Ptosis
- Pupil may be dilated (sometimes called a 'surgical' third nerve palsy) → PCA aneurysm

Causes

- Diabetes Mellitus
- Vasculitis e.g. Temporal arteritis, SLE
- False localizing sign due to uncal herniation through tentorium if raised ICP
- Posterior communicating artery aneurysm (pupil dilated)
- Cavernous sinus thrombosis
- **Weber's syndrome: ipsilateral third nerve palsy with contralateral hemiplegia -caused by midbrain strokes (cerebral peduncle)**
- Other possible causes: amyloid, multiple sclerosis



Myasthenia Gravis: Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. **Antibodies to acetylcholine receptors** are seen in 90% of cases (antibodies are less commonly seen in disease limited to the ocular muscles). Myasthenia is more common in women (2:1). It is a neuromuscular disease leading to fluctuating muscle weakness and fatiguability, in which weakness is caused by circulating antibodies that block acetylcholine receptors at the post-synaptic neuromuscular junction. At 200–400 cases per million it is one of the less common autoimmune disorders. The most common exacerbating factor is exertion resulting in fatigability, which is the hallmark feature of myasthenia gravis. Symptoms become more marked during the day

Features

- Extraocular muscle weakness: diplopia
- Proximal muscle weakness: face, neck, limb girdle
- Ptosis
- Dysphagia

Associations

- Thymomas in 15%
- Autoimmune disorders: pernicious anemia, hypothyroidism, rheumatoid, SLE
- Thymic hyperplasia in 50-70%

Investigations

- Tensilon test: IV edrophonium ↓ muscle weakness temporarily
- CT thorax to exclude thymoma
- CK normal

Management

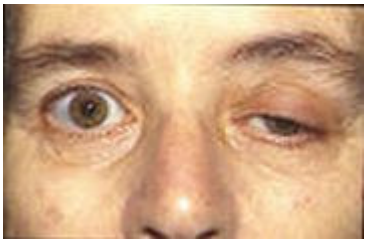
- Long-acting anticholinesterase e.g. Pyridostigmine
- Immunosuppression: prednisolone initially (although sometimes it can worsen the symptoms)
- Thymectomy

Management of myasthenic crisis

- Plasmapheresis
- Intravenous immunoglobulins

The following **drugs may exacerbate myasthenia**:

- β-blockers (theoretical worsening based on propensity to cause side effects of fatigue and weakness)
- Gentamicin, Aminoglycosides and Tetracyclin
- Lithium
- Magnesium
- Penicillamine
- Phenytoin
- Quinidine, procainamide, verapamil, contrast agents.
- Chloroquine
- Prednisolone



Lambert-Eaton Myasthenic Syndrome is seen in association with small cell lung cancer, and to a lesser extent breast and ovarian cancer. It may also occur independently as an autoimmune disorder. Lambert-Eaton myasthenic syndrome is caused by an antibody directed against pre-synaptic voltage gated calcium channel in the peripheral nervous system

Features

- Repeated muscle contractions lead to ↑ muscle strength* (in contrast to myasthenia gravis)
- Limb girdle weakness (affects lower limbs first). Proximal muscles more commonly affected.
- Hyporeflexia
- Autonomic symptoms: dry mouth, impotence, difficultly micturating
- Ophthalmoplegia and ptosis not commonly a feature (unlike in myasthenia gravis)

EMG

- Incremental response to repetitive electrical stimulation

Management

- Treatment of underlying cancer
- Immunosuppression, for example with prednisolone and/or azathioprine
- 3,4-diaminopyridine is currently being trialled**
- Intravenous immunoglobulin therapy and plasma exchange may be beneficial

*in reality this is seen in only 50% of patients and following prolonged muscle use muscle strength will eventually ↓
**works by blocking potassium channel efflux in the nerve terminal so that the action potential duration is ↑. Calcium channels can then be open for a longer time and allow greater acetylcholine release to stimulate muscle at the end plate.

Paraneoplastic Syndromes Affecting Nervous System

Lambert-Eaton myasthenic syndrome

- Associated with small cell lung cancer (also breast and ovarian)
- Antibody directed against pre-synaptic voltage gated calcium channel in PNS
- Can also occur independently as autoimmune disorder
- ↑ muscle strength followed by weakness eventually.

Anti-Hu (imagine H sticks as 2 lungs or 2 brain hemispheres)

- Associated with small cell lung carcinoma and neuroblastomas
- Sensory neuropathy - may be painful
- Cerebellar syndrome
- Encephalomyelitis

Anti-Yo (imagine Y as lady's private organ)

- Associated with ovarian and breast cancer
- Cerebellar syndrome

Anti-GAD antibody

- Associated with breast, colorectal and small cell lung carcinoma
- **Stiff person's** syndrome or diffuse hypertonia

Anti-Ri

- Associated with breast and small cell lung carcinoma
- Ocular opsoclonus-myoclonus

Paraneoplastic Cerbellar Syndrome: It is believed to be due to an autoimmune reaction targeted against components of the central nervous system (specifically Purkinje cells and large brain stem nuclei). It is thought to be caused by an anti-neuronal Antibody known as anti-Yo.

It typically presents as a subacute progressive cerebellar ataxia, both truncal and appendicular.

Loss of corneal reflex - think acoustic neuroma

Acoustic Neuromas account for approximately 5% of intracranial tumours and 90% of cerebellopontine angle. AKA **Vestibular schwannoma,** it is a benign primary intracranial tumor of the myelin-forming cells of the vestibulocochlear nerve (CN VIII). The term "acoustic" is a misnomer, as the tumor rarely arises from the acoustic (or cochlear) division of the vestibulocochlear nerve

Features can be predicted by the affected cranial nerves

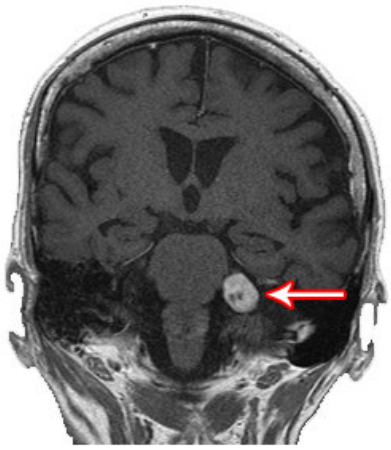
- Cranial nerve VIII: hearing loss, vertigo, tinnitus
- Cranial nerve V: absent corneal reflex
- Cranial nerve VII: facial palsy

Bilateral acoustic neuromas are seen in neurofibromatosis type 2

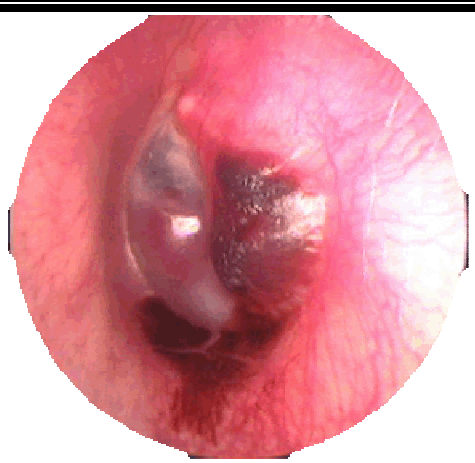
MRI of the cerebellopontine angle is the investigation of choice

Glomus Jugulare Tumours are slow-growing, highly vascular tumours derived from neural tissue and arising within the jugular foramen of the temporal bone.

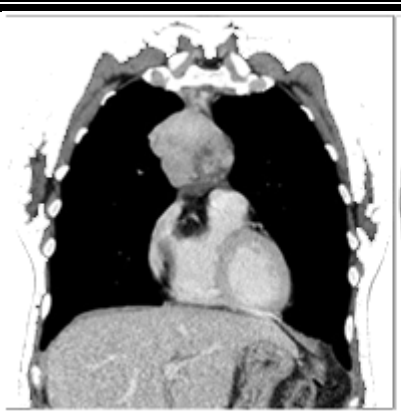
- ♀:♂ ratio between 3 and 6:1 - Annual incidence is around 1 in 1.3 million.
- Tend to present between 40 and 70 years of age.
- Presents with deafness and pulsatile tinnitus
- Rarely causes hearing loss (4%) with vertigo (if extends to middle ear)
- Cranial nerves IX to XI pass through the jugular foramen, and so are commonly involved.
- Less commonly, affect cranial nerves VII and XII.
- Otoscopic examination may reveal a characteristic pulsatile reddish-blue mass behind the tympanic membrane.
- Surgical resection is the treatment of choice, embolisation and radiotherapy have been used.

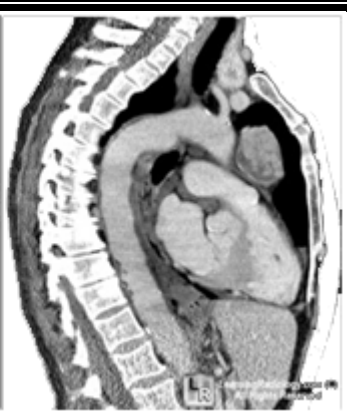


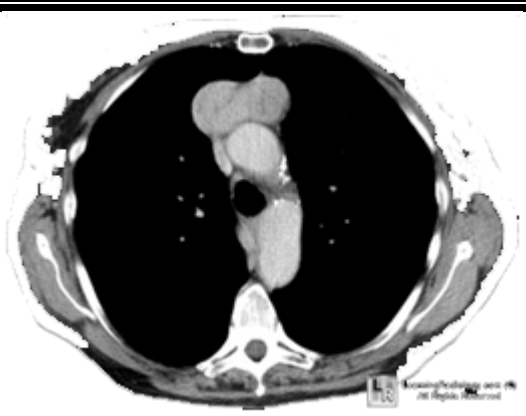
Cerebellopontine angle tumor (Acoustic Neuroma)



Otoscopy showing Glomus tumor







Thymoma on CT Thorax

Peripheral Neuropathy:

Demyelinating pathology	Axonal pathology
• Guillain-Barre syndrome • Chronic inflammatory demyelinating polyneuropathy (CIDP) • Amiodarone • Hereditary sensorimotor neuropathies (HSMN) type I • Paraprotein neuropathy	• Alcohol • Diabetes mellitus (±demyelinating picture) • Vasculitis • Vit. B12 deficiency (±demyelinating picture) • Hereditary sensorimotor neuropathies (HSMN) type II

Predominately motor loss	Predominately sensory loss
• Guillain-Barre syndrome • Porphyria • Lead poisoning • HSMN - Charcot-Marie-Tooth • CIDP • Diphtheria	• Diabetes • Uremia • Leprosy • Alcoholism • Vitamin B12 deficiency • Amyloidosis

Alcoholic neuropathy

- Secondary to both direct toxic effects and ↓ absorption of B vitamins
- Sensory symptoms typically present prior to motor symptoms

Vitamin B12 deficiency

- Subacute combined degeneration of spinal cord
- Dorsal column usually affected first (joint position, vibration) prior to distal paraesthesia

Drugs causing a peripheral neuropathy

- Antibiotics: nitrofurantoin, metronidazole
- Amiodarone
- Isoniazid
- Vincristine and most of the anti-cancer chemotherapy
- Tricyclic antidepressants

Nerve Conduction Studies (NCS) are useful to determine axonal/demyelinating pathology

Demyelinating	Axonal
• **Reduced conduction velocity** • **Normal amplitude**	• **Normal conduction velocity** • **Reduced amplitude**

Autonomic Neuropathy

Features	Causes
• Impotence, inability to sweat • Postural hypotension e.g. Drop of 30/15 mmHg • Loss of ↓ in heart rate following deep breathing • Pupils: dilates following adrenaline instillation	• Diabetes • Guillain-Barre syndrome • Multisystem atrophy (MSA), Shy-Drager • Parkinson's • Infections: HIV, Chagas', neurosyphilis • Drugs: antihypertensives, tricyclics • Craniopharyngioma

Guillain-Barre Syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically Campylobacter jejuni). **It is usually a subacute neuropathy.**

Pathogenesis

- Cross reaction of antibodies with gangliosides in the peripheral nervous system
- Correlation between anti-ganglioside antibody (e.g. Anti-GM1) and clinical features has been demonstrated
- Anti-GM1 antibodies in 25% of patients

Periciptating Organisms:

- Campylobacter jejuni
- Chlamydia
- HBV
- Mycoplasma Pneumoniae
- CMV, EBV, HZV, HIV

Presentation:

- Usually presents subacutely (over days to weeks) as an ascending paralysis noted by weakness in the legs that spreads to the upper limbs and the face along with complete loss of deep tendon reflexes. It may involve respiratory muscles leading to their paralysis.

Management

- Plasma exchange
- IV immunoglobulins
- Steroids and immunosuppressants have not been shown to be beneficial
- **FVC regularly to monitor respiratory function**

Prognosis

- 20% suffer permanent disability, 5% die

Poor prognostic features

- Age > 40 years
- Poor upper extremity muscle strength
- Rapid symptoms progression.
- Previous history of a diarrhoeal illness (specifically *campylobacter jejuni*)
- High anti-GM1 antibody titre
- Need for ventilatory support

There is currently contradictory evidence as to whether a gradual or rapid onset of GBS is associated with a poor outcome

Miller-Fisher syndrome

- Variant of Guillain-Barre syndrome
- Associated with areflexia, ataxia, ophthalmoplegia
- Usually presents as a descending paralysis rather than ascending as seen in other forms of Guillain-Barre syndrome
- Anti-GQ1b antibodies are present in 90% of cases

Herpes Simplex (HSV) Encephalitis is a common topic in the MRCP. The virus characteristically affects the temporal lobes - questions may give the result of imaging or describe temporal lobe signs e.g. aphasia

Features

- Fever, headache, psychiatric symptoms, seizures, vomiting
- Focal features e.g. Aphasia
- Peripheral lesions (e.g. Cold sores) have no relation to presence of HSV encephalitis

Pathophysiology

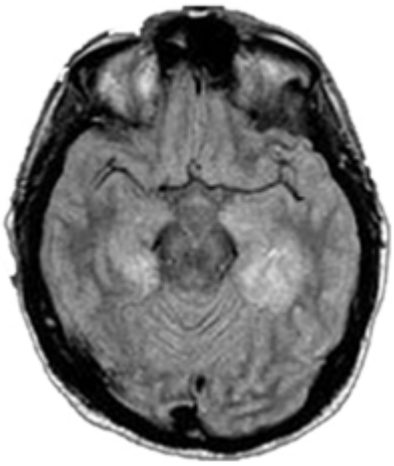
- HSV-1 responsible for 95% of cases in adults
- Typically affects temporal and inferior frontal lobes

Investigation

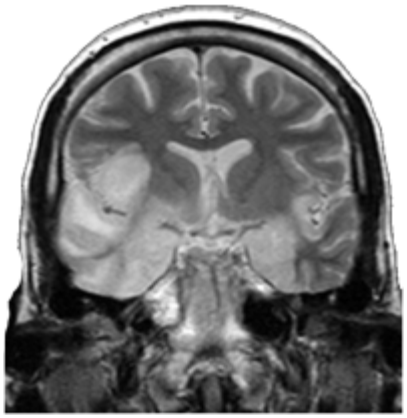
- CSF: lymphocytosis, elevated protein
- PCR for HSV
- CT: medial temporal and inferior frontal changes (e.g. Petechial hemorrhages) - normal in one-third of patients
- MRI is better
- EEG pattern: lateralised periodic discharges (LPD, not LAPD☺) at 2 Hz

Treatment

- IV aciclovir



Bilateral **herpes simplex encephalitis** changes in CT

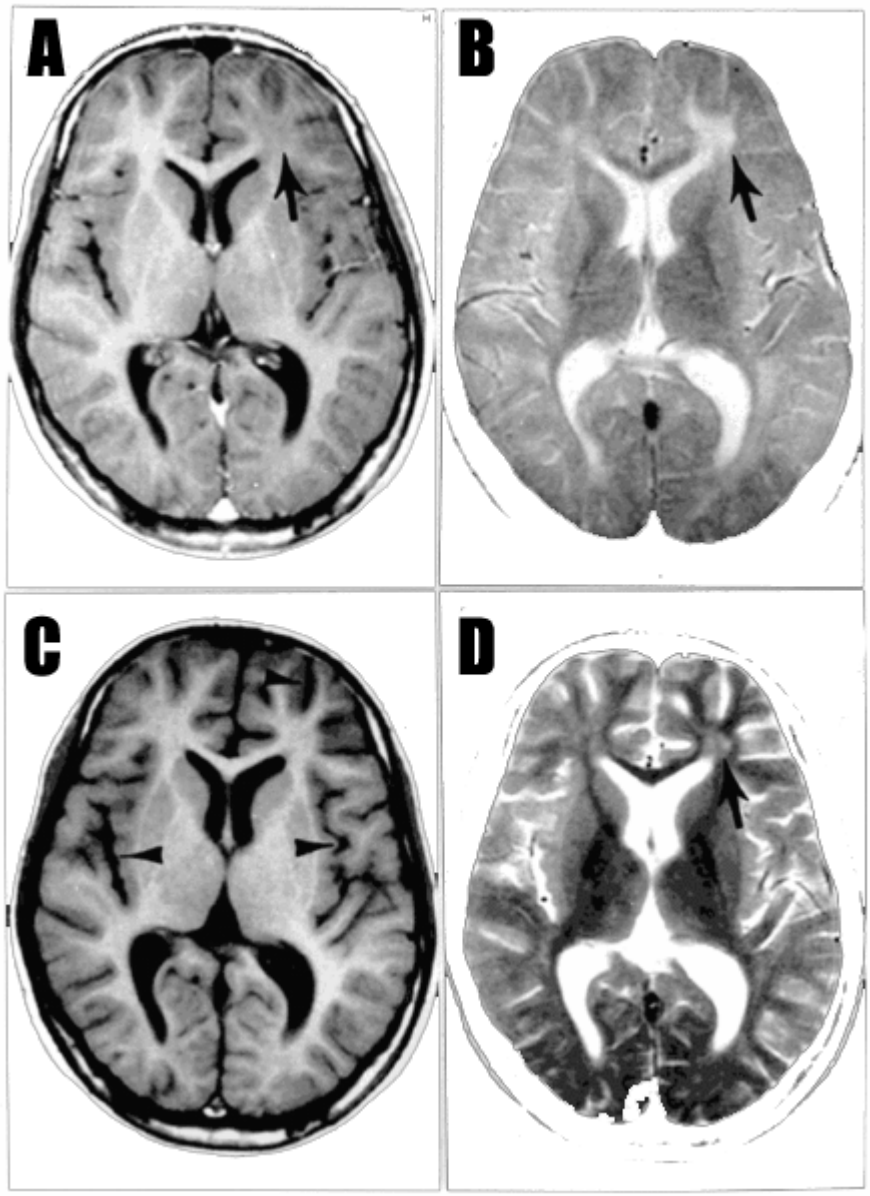


MR brain scan showing changes in temporal lobe due to oedema and hemorrhage in **herpes simplex encephalitis**.

The prognosis is dependent on whether aciclovir is commenced early. If treatment is started promptly the mortality is 10-20%. Left untreated the mortality approaches 80%

Sub-acute Sclerosing Panencephalitis: It is recognized to be the result of chronic measles infection. It is now an uncommon disease after the widespread use of measles vaccination. There is usually a history of measles very early in life followed by 8 years of asymptomatic period.

- Evolves in several stages.
    - Initially: decline in proficiency in school.
    - Followed by diffuse myoclonic jerks in association with focal and generalised seizures and visual deterioration due to choiroidoretinitis.
    - Followed by pyramidal signs, rigidity and progressive unresponsiveness.
    - Finally the patient lies decorticated followed by death.
- The course of the illness is 1 to 3 years. No effective treatment is available



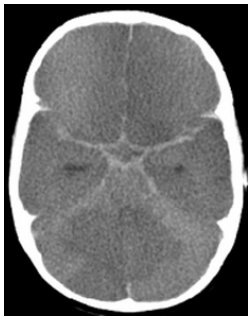
Subacute sclerosing panencephalitis: MRI scans of the brain at the time of presentation in the neurology clinic (A and B) and 3 months later (C and D). Panels A and C are T1-weighted images; B and D are T2-weighted images. The initial MRI scan (A and B) reveals a focal abnormality in the subcortical white matter of the left frontal lobe, consisting of a hypointense signal on the T1-weighted image (arrow in A) and a hyperintense signal on the T2-weighted image (arrow in B). In the followup scan, the focal abnormality in the left frontal lobe is less obvious than previously (arrow in D), but advanced and diffuse cortical atrophy is present, signified by the ventriculomegaly and markedly enlarged sulci (arrowheads in C)

HIV Neurocomplications:

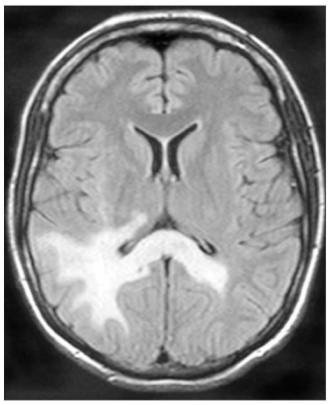
Generalised neurological disease:

1. Encephalitis
   - May be due to CMV or HIV itself
   - HSV encephalitis but is relatively rare in the context of HIV
   - CT: **edematous brain**

2. *Cryptococcus*
   - Most common fungal infection of CNS
   - Headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
   - CSF: high opening pressure, India ink test positive
   - **CT: meningeal enhancement, cerebral edema →**
   - Meningitis is typical presentation but may occasionally cause a space occupying lesion



3. Progressive multifocal leukoencephalopathy (PML)
   - Widespread demyelination
   - Due to infection of oligodendrocytes by human papovirus (jc virus)
   - Symptoms, subacute onset : behavioural changes, speech, motor, visual impairment
   - CT: single or multiple lesions, no mass effect, don't usually enhance, **Low attenuation diffusely**
   - MRI is better - high-signal demyelinating white matter lesions are seen in advanced HIV.

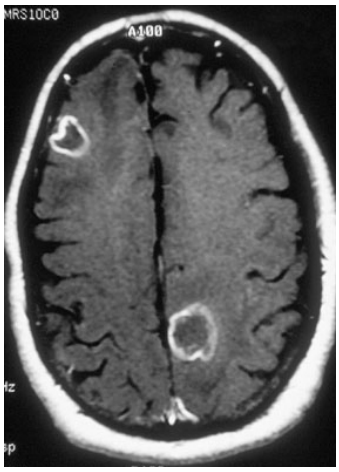


MRI: T2-weighted. Lesions involve the temporal/occipital lobes and corpus callosum. Lesions are hyperintense on the T2-weighted image. There was no abnormal enhancement with gadolinium, and no mass effect.

4. AIDS dementia complex
   - Caused by HIV virus itself
   - Symptoms: behavioural changes, motor impairment
   - **CT: cortical and subcortical atrophy**

Focal neurological lesions:

1. Toxoplasmosis
   - Accounts for around 50% of cerebral lesions in patients with HIV
   - Constitutional symptoms, headache, confusion, drowsiness
   - CT: usually single or **multiple ring enhancing lesions**, mass effect may be seen
   - Management: sulfadiazine and pyrimethamine



Contrast CT showing typical multiple ring-enhancing lesions of Toxoplasmosis.

2. Primary CNS lymphoma
   - Accounts for around 30% of cerebral lesions
   - Associated with the Epstein-Barr virus
   - CT: **single** or multiple **ring enhancing lesion**s

3. Tuberculosis
   - Much less common than toxoplasmosis or primary lymphoma
   - CT: Single enhancing lesion

Dystrophia myotonica - **D**M1	
• **D**istal weakness initially • autosomal **D**ominant	• **D**iabetes • **D**ysarthria

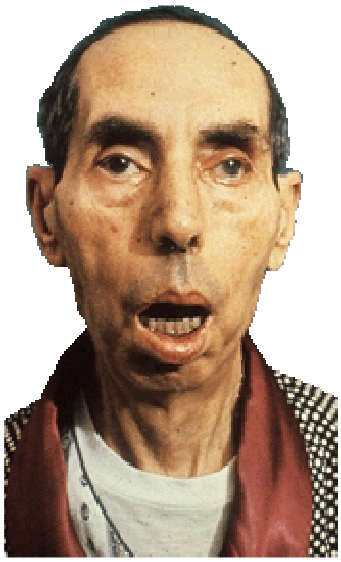
Myotonic dystrophy (also called dystrophia myotonica) is an inherited myopathy with features developing at around 20-30 years old. It affects skeletal, cardiac and smooth muscle. There are two main types of myotonic dystrophy, DM1 and DM2.

Genetics

- Autosomal dominant
- A trinucleotide repeat disorder
- DM1 is caused by a CTG repeat at the end of the DMPK (Dystrophia Myotonica-Protein Kinase) gene on chromosome 19
- DM2 is caused by a repeat expansion of the ZNF9 gene on chromosome 3

The key differences are listed in table below:

DM1	DM2
- DMPK gene on chromosome 19 - Distal weakness more prominent	- ZNF9 gene on chromosome 3 - Proximal weakness more prominent - Severe congenital form is not seen



Slow-relaxing grip may be noticed on initial hand-shake with the patient and is typical of myotonic dystrophy. Dysarthric speech is secondary to myotonia of the tongue and pharynx

General features (typically in the above figure)

- Myotonic facies (long, 'haggard' appearance)
- Frontal balding
- **Bilateral ptosis**
- Cataracts
- Dysarthria

Other features

- Myotonia (tonic spasm of muscle)
- Weakness of arms and legs (distal initially)
- Mild mental impairment
- Diabetes mellitus
- **Testicular atrophy**
- **Cardiac involvement: heart block, cardiomyopathy**
- Dysphagia

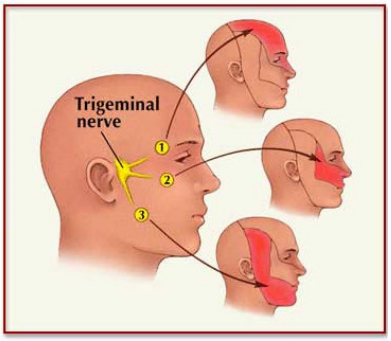
Spastic Paraparesis: describes a upper motor neuron pattern of weakness in the lower limbs

Causes

- Demyelination e.g. Multiple sclerosis
- Cord compression: trauma, tumour
- Parasagittal meningioma
- Tropical spastic paraparesis
- Hereditary spastic paraplegia
- Transverse myelitis e.g. HIV
- Syringomyelia
- Osteoarthritis of the cervical spine

Trigeminal neuralgia is a pain syndrome characterized by severe unilateral pain. The vast majority of cases are idiopathic but compression of the trigeminal roots by tumours or vascular problems may occur. The International Headache Society defines trigeminal neuralgia as:

- A unilateral disorder characterized by brief electric shock-like pains, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve
- The pain is commonly evoked by light touch, including washing, shaving, smoking, talking, and brushing the teeth (trigger factors), and frequently occurs spontaneously
- Small areas in the nasolabial fold or chin may be particularly susceptible to the precipitation of pain (trigger areas)
- The pains usually remit for variable periods



Management

- Carbamazepine (Tegretol®) is first-line
- Failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology

2010 NICE neuropathic pain guidelines recommend using amitriptyline or pregabalin first-line for non-diabetic neuropathic pain., but makes no specific recommendation for trigeminal neuralgia. Due to the amount of evidence supporting carbamazepine in trigeminal neuralgia and its recommendation in consensus guidelines (including Clinical Knowledge Summaries)

Neuropathic pain: may be defined as pain which arises following damage or disruption of the nervous system. It is often difficult to treat and responds poorly to standard analgesia.

Examples include:

- Diabetic neuropathy
- Post-herpetic neuralgia
- Trigeminal neuralgia
- Prolapsed intervertebral disc

NICE issued guidance in 2010 on the management of neuropathic pain:

- First-line treatment*: oral amitriptyline or pregabalin
- If satisfactory pain reduction is obtained with amitriptyline but the person cannot tolerate the

adverse effects, consider oral imipramine or nortriptyline as an alternative

- Second-line treatment: if first-line treatment was with amitriptyline, switch to or combine with pregabalin. If first-line treatment was with pregabalin, switch to or combine with amitriptyline
- Other options: pain management clinic, tramadol (not other strong opioids), topical lidocaine for localised pain if patients unable to take oral medication

*please note that for some specific conditions the guidance may vary. For example carbamazepine is used first-line for trigeminal neuralgia, duloxetine for diabetic neuropathy

NICE updated it's guidance on the management of diabetic neuropathy in 2010:

- First-line: oral duloxetine. Oral amitriptyline if duloxetine is contraindicated.
- Second-line treatment: if first-line treatment was with duloxetine, switch to amitriptyline or pregabalin, or combine with pregabalin. If first-line treatment was with amitriptyline, switch to or combine with pregabalin
- Other options: pain management clinic, tramadol (not other strong opioids), topical lidocaine for localised pain if patients unable to take oral medication

Cluster headaches* are more common in men (5:1) and smokers

Episodic eye pain, lacrimation, nasal stuffiness occurring daily - cluster headache

Features

- Pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours
- Clusters typically last 4-12 weeks
- Intense pain around one eye (recurrent attacks 'always' affect same side)
- Patient is restless during an attack
- Accompanied by redness, lacrimation, lid swelling
- Nasal stuffiness
- Miosis and ptosis in a minority

Cluster headaches may involve pain around one eye, along with drooping of the lid, tearing and congestion on the same side as the pain

A.D.A.M.

Management

- Acute: 100% oxygen, subcutaneous sumatriptan (5-HT1D receptor agonist), nasal lidocaine
- Prophylaxis: verapamil, prednisolone
- Consider specialist referral

*some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin.

Chronic Paroxysmal Hemicrania (CPH):

Characterized by:

- Unilateral pain which is generally oculofrontotemporal in location.
- Can occur at any time, and patients often describe a throbbing, boring, pulsating or claw-like pain
- Frequency of attacks is usually 10–20 per day. Episodes usually last 2–25 min, but may last as long as 60 min
- Patients may also complain of ipsilateral conjunctival injection, ptosis and lid swelling, lacrimation and rhinorrhoea, occasionally photophobia
- The most effective treatment is with indomethacin

The most important differential diagnosis is from cluster headache (CH) and from other headache syndromes characterized by autonomic dysfunction such as SUNCT (short-lasting unilateral neuralgiform headache with conjunctival injection and tearing). CH has male preponderance, unlike CPH, which is more common in females. In CPH, frequency of attacks is higher, usually more than 15 in 24 hours, whereas CH has an attack frequency of 1-4 (maximum 8) in 24 hours. The duration of headaches is shorter in CPH (2-25 min) than in CH (15-60 min).

Migraine: The International Headache Society has produced the following diagnostic criteria for migraine without aura:

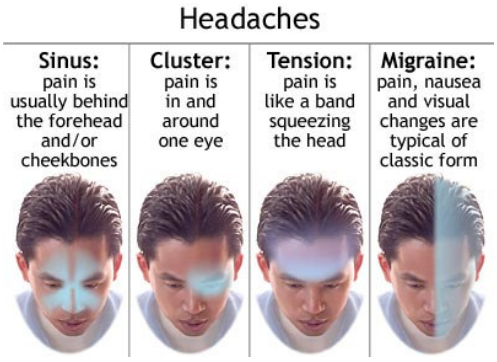
A	At least 5 attacks fulfilling criteria B-D
B	Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated)
C	Headache has at least two of the following characteristics: 1. Unilateral location* 2. Pulsating quality (i.e., varying with the heartbeat) 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D	During headache at least one of the following: 1. Nausea and/or vomiting* 2. Photophobia and phonophobia
E	Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder)

*In children, attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

Migraine with aura (around 1 in 3 migraine patients) tends to be easier to diagnose with a typical aura being progressive in nature and may occur hours prior to the headache. Typical aura include a transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent'). Sensory symptoms may also occur

ACute: 5-HT1 **AG**onist prophylaxis: β-blocker, 5-HT2 antagonist	Epilepsy is not a contraindication to the use of triptans. Opioids are not recommended in the management of migraine

Acute treatment: Standard analgesia, Triptans & Ergotamine.



Standard analgesia

- First-line therapy
- E.g. Paracetamol, ibuprofen, aspirin, may be poorly absorbed, often combined with anti-emetic e.g. Metoclopramide (to relieve associate nausea) → caution should be exercised with young patients as acute dystonic reactions may develop

Avoid aspirin in children < 16 years as risk of Reye's syndrome

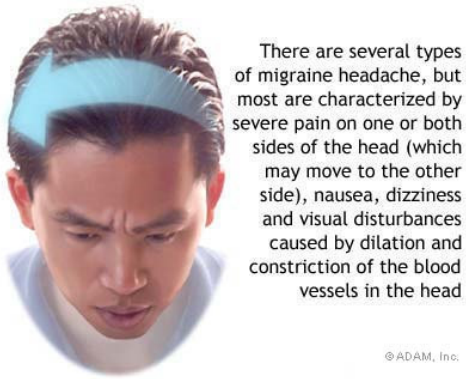
Triptans

- Second-line therapy
- Specific 5-HT1 agonists - opposes Vasodilation

Ergotamine

- α-blocker and a partial 5-HT1 agonist
- Now rarely used due to high incidence of adverse effects (e.g. Nausea and vomiting)
- Listed in the BNF as 'less suitable for prescribing'

Prophylaxis should be given if patients are experiencing ≥ 2 attacks/month. Treatment is effective in about 60% of patients



First-line

- β-blockers: propranolol 80-240mg OD

Also recommended in the SIGN guidelines

- Sodium valproate
- Topiramate (CKS recommend this is used under specialist supervision)
- Gabapentin
- Amitriptyline
- Venlafaxine

The SIGN guidelines also suggest that stress management and acupuncture may be useful

5-HT2 antagonists

- Pizotifen: used less commonly now due to adverse effects (weight gain and drowsiness)
- Methysergide: very rarely used as associated with retroperitoneal fibrosis

Migraine during pregnancy

- Paracetamol 1g is first-line
- Aspirin 300mg or ibuprofen 400mg can be used second-line in the first and second trimester

Migraine and the combined oral contraceptive (COC) pill

- If patients have migraine with aura then the COC is **absolutely contraindicated** due to an increased risk of stroke (relative risk 8.72)

Migraine and menstruation

- Many women find that the frequency and severity of migraines increase around the time of

menstruation

- SIGN recommends that women are treated with mefanamic acid or a combination of aspirin, paracetamol and caffeine. Triptans are also recommended in the acute situation

Migraine and hormone replacement therapy (HRT)

- Safe to prescribe HRT for patients with a history of migraine but it may make migraines worse

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CSF

Normal values of cerebrospinal fluid (CSF) are as follows:

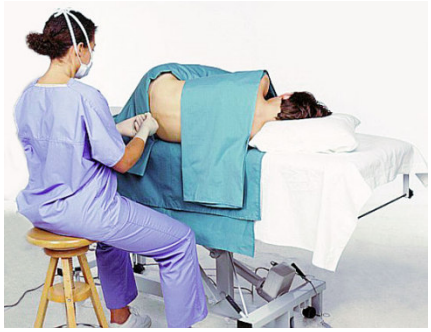
- Pressure = 60-150 mm (patient recumbent)
- Protein = 0.2-0.4 g/l
- Glucose = > 2/3 blood glucose
- Cells: red cells = 0, white cells < 5/mm³

The following conditions are associated with raised lymphocytes

- Viral meningitis/encephalitis
- TB meningitis
- **Partially treated bacterial meningitis**
- **Lyme disease**
- **Behcet's, SLE**
- Lymphoma, leukemia

The following conditions are associated with raised protein levels

- Tuberculous, fungal and bacterial meningitis
- Viral encephalitis
- Guillain-Barre syndrome
- Spinal block (Froin's syndrome)



Lumbar Puncture

Headache following Lumbar Puncture (LP) occurs in approximately one-third of patients. The pathophysiology is unclear but may relate to a 'leak' of CSF following dural puncture. Post-LP headaches are more common in young ♀ with a low BMI.

Typical features

- Usually develops within 24-48 hours following LP but may occur up to one week later
- May last several days
- Worsens with upright position
- Improves with recumbent position

Factors which may contribute to headache	Factors which do not contribute to headache
↑ needle size Direction of bevel Not replacing the stylet ↑ number of LP attempts	↑ volume of CSF removed Bed rest following procedure ↑ fluid intake post procedure Opening pressure of CSF Position of patient

Management

- Supportive initially (analgesia, rest)
- If pain continues for more than 72 hours then specific treatment is indicated, to prevent subdural hematoma
- Treatment options include: blood patch, epidural saline and intravenous caffeine

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Oppenheim's sign is seen when scratching of the inner side of leg leads to extension of the toes. It is a sign of cerebral irritation

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EMG common findings:

- Polumyositis: reduced ampliyude and duration of motor unit
- MND: fibrillation due to denervation
- Myasthenia Gravis: diminished responses to repitative stimulations
- Lambert Eaton Myasthenia: enhanced responses to repitative stimulations.
- Myotonia Dystophia: High frequency action potentioals, Kamikaze discharge or dive bombers frequency which is heard

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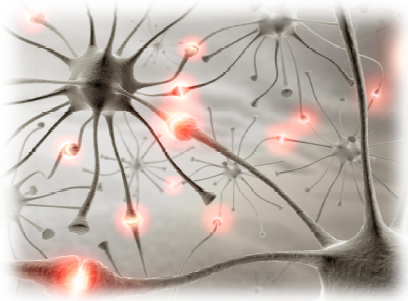
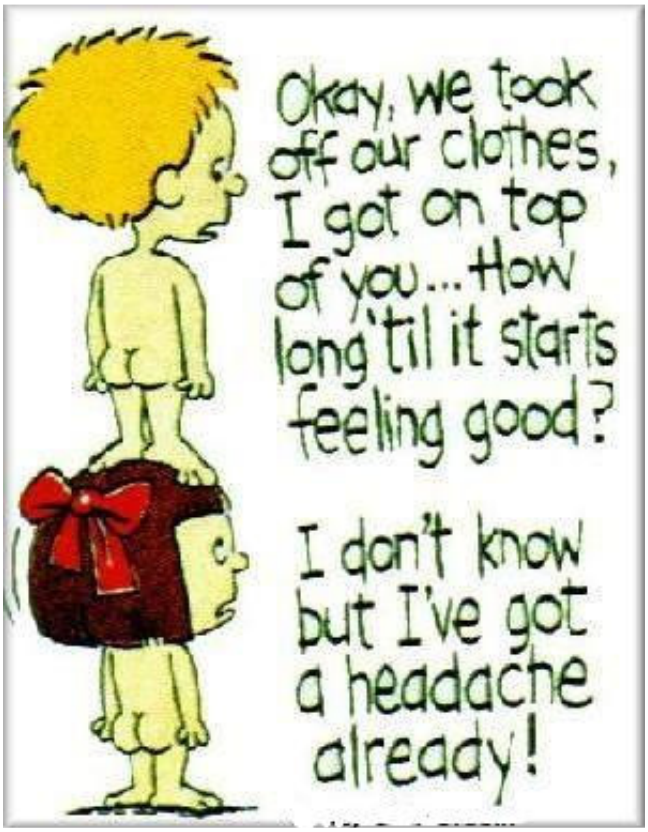
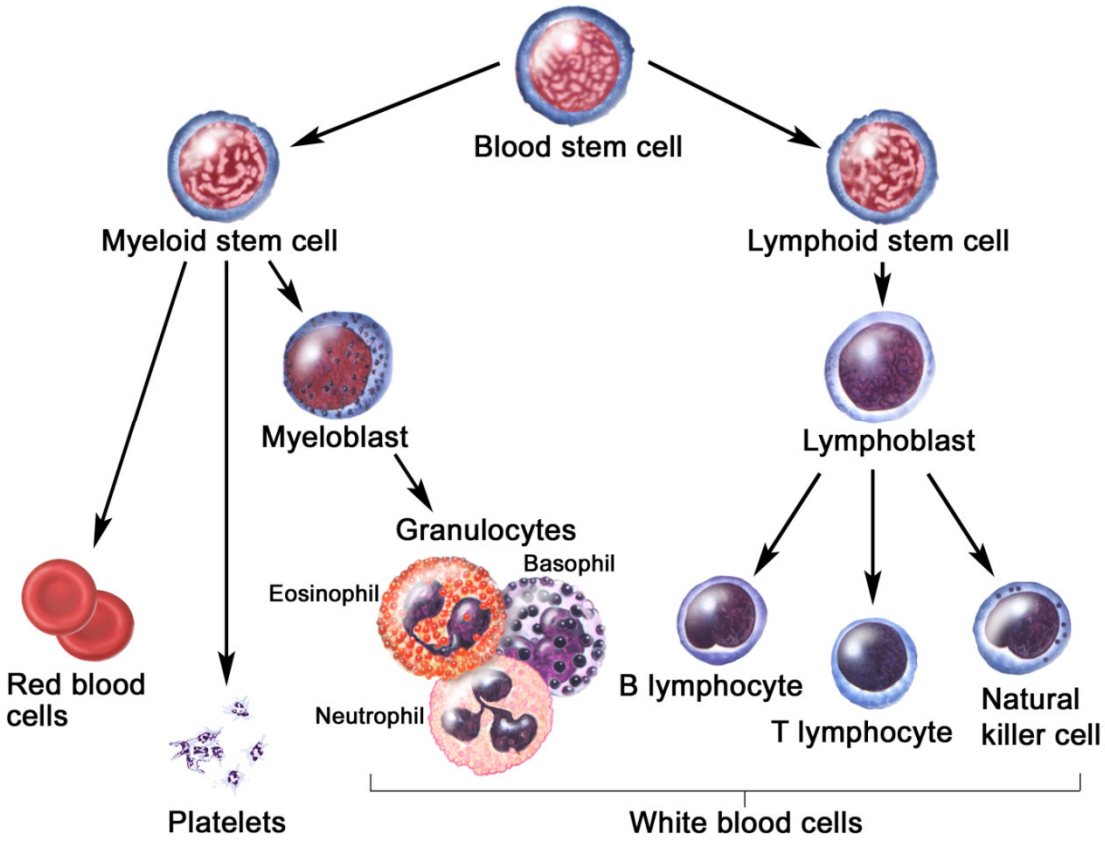



Now I know why they call it ICU!


Okay, we took off our clothes, I got on top of you... How long 'til it starts feeling good?
I don't know but I've got a headache already!

HEMATOLOGY


Blood stem cell
Myeloid stem cell
Lymphoid stem cell
Myeloblast
Lymphoblast
Granulocytes
Basophil
Eosinophil
Neutrophil
Red blood cells
Platelets
B lymphocyte
T lymphocyte
Natural killer cell
White blood cells

Important Drugs in Hemato-Oncology:

Cytotoxic/Drug*	Mechanism of action	Adverse effects
Vincristine	Inhibits formation of microtubules, mitotsis inhibitor **(M stage of cell cycle)**	Peripheral neuropathy (reversible)
Cisplatin	Causes **C**ross-linking in DNA	Ototoxicity, peripheral neuropathy, **hypomagnesemia**
Bleomycin	Degrades preformed DNA	Lung fibrosis
Doxorubicin	Stabilizes DNA-topoisomerase II complex. Inhibits DNA & RNA synthesis	Cardiomyopathy
Methotrexate	Inhibits dihydrofolate reductase and thymidylate synthesis	Myelosuppression, mucositis
Cyclophosphamide	Alkylating agent - causes **C**ross-linking in DNA	Hemorrhagic cystitis (incidence ↓ by the use of hydration and mesna), myelosuppression, transitional cell carcinoma
Docetaxel	Prevents microtubule depolymerisation & disassembly, decreasing free tubulin	Neutropaenia + peripheral neuropathy
Imatinib*	Inhibitor of the tyrosine kinase associated with the BCR-ABL defect →CML	Edema, nausea, rash and musculoskeletal pain are common but mild. Severe congestive cardiac failure is an uncommon but recognized side effect
interferon-α*	Cytokines released by the body in response to viral infections and neoplasia. They are classified according to cellular origin and the type of receptor they bind to. IFN-α and IFN-β bind to type 1 receptors whilst IFN-gamma binds only to type 2 receptors. IFN-α is produced by leucocytes and has an antiviral action USES: CML, Hairy cell Leukemia, hepatitis B & C, Kaposi's sarcoma, metastatic renal cell cancer.	The most frequent adverse effects are **flu-like symptoms** and **depression**. Erythema, pain and hardness on the spot of injection are also frequently observed. Interferon therapy causes immunosuppression, in particular through **neutropenia** and can result in some infections manifesting in unusual ways

Extravasation of chemotherapy: extravasation should be suspected if a patient complains of pain, burning, swelling or redness at the site of the infusion cannula.

Management:

- Immediate management would consist of stopping the infusion, immobilizing the arm and attempting to aspirate any accessible drug from the cannula and extravasation site before removal of the cannula.
- Agent specific antidotes can be given after receiving specialist advice. Cold compresses are generally applied except in the case of vinca alkaloids in which case a heat compress should be applied.
- Doxorubicin or daunorubicin extravasation injuries are particularly prone to causing ulceration, particularly on the back of the hand and hence a plastic surgery consultation is likely to be needed, Use topical corticosteroids to treat the site of inflammation.Consider reporting to the National Extravasation Information Service.

Transfusion Reactions:

Tips:

- Bacterial contamination is very rare with red cell transfusions and more common with platelet transfusions (which are stored at room temperature).
- IgG antibodies cause delayed extravascular hemolytic transfusion reactions much more commonly than acute intravascular reactions.
- IgM anti-A and anti-B antibodies cause acute hemolytic transfusion reactions. As little as 4 mm of transfused ABO incompatible blood can be fatal.
- ABO antigens are present from birth, whereas ABO antibodies are usually acquired in the first 6 months of life.
- Anti-O antibodies do not exist.
- About 1 in 10 000 people are deficient in IgA and can form clinically significant, complement binding, antibodies to IgA.
- In many cases of apparent anaphylaxis to a blood transfusion, the causative agent is unknown, but is putatively thought to be due to allergens in the donation, such as penicillin or peanut antigens.

Delayed Transfusion Reactions: occur 5-10 days post transfusion due to the development of red cell alloantibodies:

- **Clinical features:** usually minimal but can include unexplained pyrexia, jaundice or unexplained drop in hemoglobin.
- **Diagnosis:** Urinalysis shows urobilinogenuria and a blood shows fragile ballooned spherocytes, diagnosis is confirmed by Coombs test which is done by adding antihuman globulin (AHG) (anti-Ig G and anticomplement) to the patient's washed RBCs. A positive test results in red cell agglutination.

Intra/Extra vascular Hemolysis

Intravascular hemolysis free hemoglobin is released which binds to haptoglobin. As haptoglobin becomes saturated hemoglobin binds to albumin forming methaemalbumin (detected by Schumm's test). Free hemoglobin is excreted in the urine as hemoglobinuria and hemosiderinuria.
Causes:

- Mismatched blood transfusion
- G6PD deficiency
- Red cell fragmentation: heart valves, TTP, DIC, HUS
- Paroxysmal nocturnal hemoglobinuria
- **Cold autoimmune hemolytic anemia**

Extravascular hemolysis: causes (usually abnormal RBCs shape)

- Hemoglobinopathies: sickle cell, thalassemia
- Hereditary spherocytosis
- Hemolytic disease of newborn
- **Warm autoimmune hemolytic anemia**

Autoimmune hemolytic anemia (AIHA) may be divided in to 'cold' and 'warm' types, according to at what temperature the antibodies best cause hemolysis. It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs. AIHA is characterized by a positive direct antiglobulin test (**Direct Coombs' Test**).

Cold AIHA is usually by **IgM** and causes hemolysis best at 4°C. Hemolysis is mediated by complement and is more commonly intravascular. Features may include symptoms of Reynaud's and acrocynaosis. Patients respond less well to steroids.
Causes of cold AIHA

- Neoplasia: e.g. lymphoma
- Infections: e.g. mycoplasma, EBV

Warm AIHA the antibody (usually **IgG**) causes hemolysis best at body temperature and hemolysis tends to occur in extravascular sites, for example the spleen. Management options include steroids, immunosuppression and splenectomy.

Causes of warm AIHA

- Autoimmune disease: e.g. Systemic lupus erythematosus*
- Neoplasia: e.g. Lymphoma, CLL
- Drugs: e.g. Methyldopa

* SLE can rarely be associated with a mixed-type autoimmune hemolytic anemia

Coombs Test:

Direct Coombs Test is used to detect these antibodies or complement proteins that are **bound to RBCs**; a blood sample is taken and the RBCs are washed (removing plasma) and then incubated with antihuman globulin (Coombs reagent). If this produces agglutination of RBCs, the test is positive, an indication that antibodies (and/or complement proteins) are bound to the surface of RBCs.

Indirect Coombs Test is used in prenatal testing of pregnant women, and prior to blood transfusion. It detects antibodies against RBCs that are present **unbound in the serum**. In this case, serum is extracted from the blood, and the serum is incubated with RBCs of known antigenicity. If agglutination occurs, the test is positive.

Hereditary spherocytosis

Spherocytosis gives rise to chronic hemolysis and gallstone formation. An important differential in a patient with hereditary spherocytosis would be splenic rupture

Basics

- Most common hereditary hemolytic anemia in northern Europeans
- **Autosomal Dominant** defect of RBC cytoskeleton
- Biconcave disc → spherocyte
- Red cell survival ↓, destroyed by spleen

Presentation

- E.g. Failure to thrive
- Jaundice, gallstones
- Splenomegaly
- Aplastic crisis precipitated by parvovirus infection
- Degree of hemolysis variable
- ↓ MCV - ↑ MCHC - ↑ Reticulocytes

Diagnosis

- Osmotic fragility test (spherocytes will rupture in mildly hypotonic solutions)

Management

- Folate replacement
- Splenectomy

Sickle Cell Disease is characterized by periods of good health with intervening crises. It is inherited as **Autosomal Recessive**. It s caused by mutation in β-globin chain of hemoglobin, causing hydrophilic amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the 6th position. The β-globin gene is found on the short arm of chromosome 11. The association of two wild-type α-globin subunits with two mutant β-globin subunits forms hemoglobin S (HbS).

Types:

- Sickle-cell anemia is a specific form of sickle-cell disease in which there is homozygosity for the mutation, it is also known as "HbSS", "SS disease", "hemoglobin S".
- Heterozygous: 1 sickle gene and 1 normal gene, it is known as "HbAS" or "sickle cell trait".
- Other, rarer forms of sickle-cell disease include sickle-hemoglobin C disease (HbSC), sickle beta-plus-thalassaemia (HbS/β+) and sickle beta-zero-thalassaemia (HbS/β0). These other forms of sickle-cell disease are compound heterozygous states in which the person has only one copy of the mutation that causes HbS and one copy of another abnormal hemoglobin allele.

Four main types of crises are recognised: (TASH)

- Thrombotic, 'painful crises'
- Aplastic
- Sequestration (spleen, liver and kidney)
- Hemolytic

Thrombotic crises

- Also known as painful crises or vaso-occlusive crises
- Precipitated by infection, dehydration, deoxygenation
- Infarcts occur in various organs including the bones (e.g. avascular necrosis of hip), hand-foot syndrome in children, lungs, spleen and brain.

Aplastic crises

- Caused by infection with parvovirus
- Sudden fall in hemoglobin

Sequestration crises

- Sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia
- Acute chest syndrome: dyspnea, chest pain, pulmonary infiltrates, low PO_2 - the most common cause of death in adults (Hydroxyurea ↓ the incidence of acute chest syndrome)
- The most common cause of death in childhood: infraction and infection (*Pneumococcus, Chlamydia, Mycoplasm*)

Hemolytic crises

- Rare
- Fall in hemoglobin due an increased rate of hemolysis

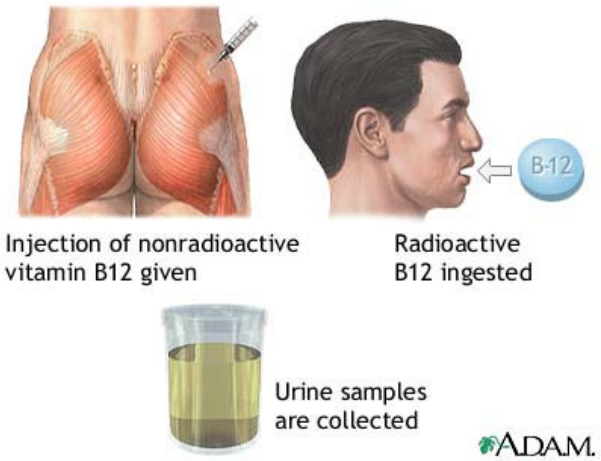
Pernicious Anemia:

Investigation

- Anti gastric parietal cell antibodies in 90% (but low specificity)
- Anti intrinsic factor antibodies in 50% (specific for pernicious anemia)
- Macrocytic anemia
- Low WBC and platelets
- LDH may be raised due to ineffective erythropoiesis
- Also low serum B12, hypersegmented polymorphs on film, megaloblasts in marrow
- Schilling test

Schilling test

- Radiolabelled B12 given on two occasions
- First on its own
- Second with oral Intrinsic Factor
- Urine B12 levels measured



Sideroblastic anemia is a condition where red cells fail to completely form heme, whose biosynthesis takes place partly in the mitochondrion. This leads to deposits of iron in the mitochondria that form a ring around the nucleus called a ring sideroblast. It may be congenital or acquired

Congenital cause:

- Delta-aminolevulinate synthase-2 deficiency

Acquired causes

- Myelodysplasia
- Alcohol
- Lead
- Chloramphenicol and Anti-TB medications (INH + Pyrazinamide)

Investigations

- Hypochromic microcytic anemia (more so in congenital)
- Bone marrow: sideroblasts and ↑ iron stores

Management

- Supportive
- Treat any underlying cause
- **Pyridoxine may help**

Pure red cell aplasia: is diagnosed when there is unexplained anaemia and reticulocytopenia, with a complete absence of red cell precursors in the bone marrow, but with preservation of other cell lines.

Assciation:

- Either spontaneously or associated with
- Thymoma
- Autoimmune
- Lymphoproliferative disorders.

Treatment is supportive with immunosuppression with cyclosporin or related compounds. The condition can rarely occur where recombinant erythropoietin is administered, where antierythropoietin antibodies can be detected; these patients respond to withdrawal of erythropoietin with subsequent falling of the antibody levels

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the commonest red cell enzyme defect. It is more common in people from the Mediterranean and Africa and is inherited in an **X-linked recessive** fashion. Many drugs can precipitate a crisis as well as infections and broad (fava) beans

Features

- Neonatal jaundice is often seen
- Intravascular hemolysis
- **Heinz bodies on blood films**

Diagnosis is made by using a G6PD enzyme assay

Drugs causing hemolysis

- Anti-malarials: primaquine
- Ciprofloxacin
- Sulfonamides
- Co-trimoxazole (because it contains sulfa)

Safe drugs:

- Penicillins
- Cephalosporins
- Macrolides (Azithro-Clarithro-Erythro mycins)
- Tetracyclines
- Trimethoprim

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder leading to hemolysis (mainly intravascular) of hematological cells. It is thought to be caused by ↑ sensitivity of cell membranes to complement (see below) due to a lack of glycoprotein glycosyl-phosphatidylinositol (GPI). Patients are more prone to venous thrombosis

Pathophysiology

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- Complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI
- Thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation

Features

- Hemolytic anemia
- Red blood cells, white blood cells, platelets or stem cells may be affected therefore **pancytopenia may be present**
- Hemoglobinuria: classically dark-colored urine in the morning (although has been shown to occur throughout the day)
- Thrombosis e.g. Budd-Chiari syndrome
- Aplastic anemia may develop in some patients

Diagnosis

- Flow cytometry of blood to detect low levels of CD59 and CD55 has now replaced Ham's test as the gold standard investigation in PNH
- Ham's test: acid-induced hemolysis (normal red cells would not)

Management

- Blood product replacement
- Anticoagulation
- Eculizumab, a monoclonal antibody directed against terminal protein C5, is currently being trialled and is showing promise in reducing intravascular hemolysis
- Stem cell transplantation

Polycythaemia may be relative, primary (polycythaemia Rubra Vera) or secondary

Relative causes	Primary	Secondary causes
• Dehydration • Stress: Gaisbock syndrome	• Polycythaemia Rubra Vera	• COPD • Altitude • Obstructive sleep apnoea • Excessive erythropoietin: cerebellar hemangioma, hypernephroma, hepatoma, uterine fibroids*

To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia red cell mass studies are sometimes used. In true polycythaemia the total red cell mass in males > 35 ml/kg and in women > 32 ml/kg

Erythroid Colony Studies: autonomous growth of erythroid colonies is taken as a sign of primary polycythaemia, where erythropoiesis has escaped the control of erythropoietin; erythroid colony studies are thought to have high specificity for detecting primary versus secondary polycythaemia.

* Uterine fibroids → menorrhagia → blood loss - polycythaemia is rarely a clinical problem

Polycythemia Rubra Vera (PRV) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to ↑ **RBC**s, often accompanied by ↑ **WBC** (neutrophils) and ↑ **platelets**. It has recently been established that a mutation in JAK2 is present in approximately 95% of patients with PRV and this has resulted in significant changes to the diagnostic criteria. The incidence of PRV peaks in the sixth decade **(50-60s of age)** with typical features including hyperviscosity, pruritus and splenomegaly, complications include arterial and venous thromboses. PRV showed some association with Budd-Chiari syndrome.

Polycythemia Rubra Vera - around 30% progress to myelofibrosis

Whilst a significant percentage of patients (around 5-15%) develop an acute leukemia, myelofibrosis is a more common transformation

Features

- **Hyperviscosity** (headaches, tinnitus, visual disturbance, cyanosis, joint pain)
- **Pruritus, typically after a hot bath**
- **Splenomegaly** ± Hepatomegaly
- Hemorrhage (secondary to abnormal platelet function not number)
- Plethoric appearance
- Low ESR
- Hypertension in a third of patients

Investigations:

- ↑ Hemoglobin and hematocrit
- ↑ Leucocyte alkaline phosphatase (LAP)
- Additional:
  - ± ↑ WBC and ↑ PLT
  - ± ↑ Plasma volume
  - ↑ Vitamin B12
  - ↑ Red cell mass
  - ↓ Erythropoietin level

Management

- Venesection - first line treatment
- Hydroxyurea -slight ↑ risk of secondary leukemia
- Allopurinol & Phosphorus-32 therapy

Prognosis

- Thrombotic events are a significant cause of morbidity and mortality
- 30% of patients progress to myelofibrosis
- 5-15% of patients progress to acute leukemia

Following history and examination, the British Committee for Standards in Hematology (BCSH) recommends the following tests are performed

- FBC/film (raised hematocrit; neutrophils, basophils, platelets raised in half of patients)
- JAK2 mutation
- Serum ferritin
- Renal and liver function tests

If the JAK2 mutation is negative and there is no obvious secondary causes, the BCSH suggest the following tests:

- Red cell mass
- Arterial oxygen saturation
- Abdominal ultrasound
- Serum erythropoietin level
- Bone marrow aspirate and trephine
- Cytogenetic analysis
- Erythroid burst-forming unit (BFU-E) culture

Other features that may be seen in PRV include a **low ESR and a raised leukocyte alkaline phosphotase**

Diagnosis: JAK2-positive PRV - diagnosis requires both criteria to be present

A1	High hematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted)
A2	Mutation in JAK2

JAK2-negative PRV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria

A1	Raised red cell mass (>25% above predicted) OR hematocrit >0.60 in men, >0.56 in women
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding BCR-ABL) in the hematopoietic cells
B1	Thrombocytosis (platelet count >450 * 10^9/l)
B2	Neutrophil leucocytosis (neutrophil count > 10 * 10^9/l in non-smokers; > 12.5*10^9/l in smokers)
B3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin

Neutropenia: on a routine full blood count (CBC) is one of the most common enquiries received by hematologists from primary care physicians and hospital doctors. Neutropenia is defined as an absolute peripheral blood neutrophil count of <2.0 × 10*9/l. There is a racial variation: black and Middle Eastern people may have neutrophil counts of <1.5 × 10*9/l normally.

Congenital neutropenia:

- Kostmann's syndrome
- Chediak–Higashi
- Schwachmann–Diamond syndrome
- Cyclical neutropenia

Acquired neutropenia:

- Infection: viral e.g. influenza, HIV, hepatitis, bacterial sepsis.
- Drugs: anticonvulsants (phenytoin) – anti-thyroid (carbimazole) – phenothiazines (chlorpromazine) – antibacterial agents (cotrimoxazole) – ACE-inhibitors (ramipril)
- Immune-mediated: SLE, Felty's syndrome (Rheumatoid Arthritis + Neutropenia + Splenomegaly)
- Bone marrow failure: leukaemia, lymphoma, Hematinic deficiency
- Splenomegaly: any cause

Investigations:

- Blood film
- Hematinics: factors that ↑Hb (Iron, TIBC, Vit B_{12}, Folic Acid, Vit D)
- Autoimmune profile bone marrow aspirate/trephine are indicated if there are severe or prolonged neutropenia or features suggestive of marrow failure

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Leukemoid reaction describes the presence of immature cells such as myeloblasts, promyelocytes and nucleated red cells in the peripheral blood. This may be due to infiltration of the bone marrow causing the immature cells to be 'pushed out' or sudden demand for new cells

Causes

- Severe infection
- Severe hemolysis
- Massive hemorrhage
- Metastatic cancer with bone marrow infiltration

A relatively common clinical problem is differentiating CML from a Leukemoid reaction:

Leukemoid reaction	**Chronic myeloid leukemia**
• High leukocyte alkaline phosphatase score • Toxic granulation (Dohle bodies) in the white cells • 'Left shift' of neutrophils i.e. ↑neutrophils or ≤ 3 segments of the nucleus	• Low leukocyte alkaline phosphatase score

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Myelofibrosis: myeloproliferative disorder. Overview:

- Thought to be caused by hyperplasia of abnormal megakaryocytes [bone marrow cell responsible for the production of blood thrombocytes (platelets)]
- The resultant release of platelet derived growth factor is thought to stimulate fibroblasts
- Hematopoiesis develops in the liver and spleen

Hyperplasia of megakaryocytes → ↑platelet derived growth factor → stimulate fibroblasts

Features

- E.g. Elderly person with symptoms of anemia e.g. Fatigue (the most common presenting symptom)
- Massive splenomegaly
- Hypermetabolic symptoms: weight loss, night sweats etc

Laboratory findings

- Anemia
- High WBC and platelet count early in the disease
- **'Tear-drop' poikilocytes on blood film**
- Unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed
- High urate and LDH (reflect ↑ cell turnover)

Myelodysplasia occurs mainly in the elderly, 30% transforms to AML

Presentation:

- Anaemia
- Infection
- Bleeding

} Due to pancytopenia

Investigations:

- Serial blood counts show evidence of increasing bone marrow failure
- Bone marrow shows increased cellularity.

Management:

- < 5% blasts in the bone marrow → manage conservatively.
- ↑ WBC → gentle chemotherapy.
- < 60 years old → Intensive chemotherapy

Chronic Myeloid Leukemia

The **Philadelphia chromosome is present in more than 95%** of patients with CML. It is due to a translocation between the long arm of chromosome 9 and 22 - t(9:22)(q34:q11). This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22. The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal

Presentation (40-50 years)

- Middle-age
- Anemia, weight loss
- **Splenomegaly may be marked** (lethargy, anorexia, abdominal discomfort – 75% palpable spleen)
- Hepatomegaly and lymphadenopathy are uncommon
- Spectrum of myeloid cells seen in peripheral blood
- ↓ neutrophil alkaline phosphatase
- May undergo blast transformation (AML in 80%, ALL in 20%)

Diagnosis:

- Philadelphia is confirmatory
- Peripheral blood film: (leukocytosis in all stages of differentiation within the myeloid linage)

- Basophilia is important diagnostic marker especially when Philadelphia is absent
- Monocytopenia
- Bone-marrow hypercellularity with ↑ myloid-erythroid ratio

↑ Granulocytes of all types, typically including mature myeloid cells. Basophils and eosinophils are almost universally ↑; this feature may help differentiate CML from a leukemoid reaction. A bone marrow biopsy is often performed as part of the evaluation for CML, and CML is confirmed by detecting the Philadelphia chromosome, this can be detected by routine cytogenetics, by fluorescent in situ hybridization, or by PCR for the bcr-abl fusion gene.

Management

- Hydroxyurea (also used in PRV, painful attacks in sicklers and as antiretroviral in HIV)
- Interferon- α
- Imatinib (inhibitor of tyrosine kinase)
- Allogenic bone marrow transplant (optimum management)

Philadelphia translocation, t(9:22) - good prognosis in CML, poor prognosis in AML + ALL

Imatinib

- Inhibitor of the tyrosine kinase associated with the BCR-ABL defect
- Very high response rate in chronic phase CML

Acute Myeloid Leukemia

is the **most common form of acute leukemia in adults**. It may occur as a primary disease or following a secondary transformation of a myeloproliferative disorder (e.g CML, myelofibrosis). > 30% blasts are almost diagnostic of AML.

Presentation:

- Early signs are vague and non-specific (influenza-like)
- Persistent or frequent infections (due to ↓ WBC)
- Bruising and petechiae (due to ↓ PLT)
- Splenomegaly may occur but typically mild and asymptomatic. Lymph node swelling is rare.

Symptoms are caused by Pancytopenia (↓RBC - ↓WBC - ↓PLT)

The combination of a myeloperoxidase or Sudan black stain and a non-specific esterase (NSE) stain will provide distinction of AML from ALL and in subclassification of AML in most cases.

Management:

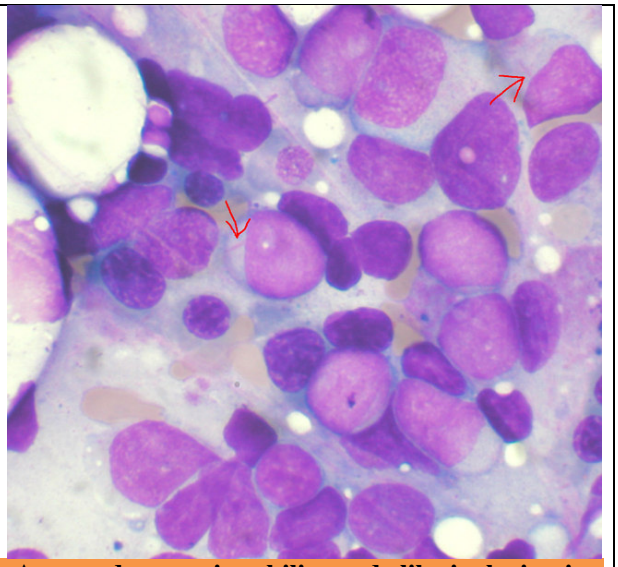
- Chemotherapy: divided into two phases:
  1. Induction: All types except M3 are given induction with cytarabine (ara-C) and an anthracycline (such as daunorubicin or idarubicin).This regimen is known as "7+3", because the ara-C is given as a continuous IVI for 7 days while the anthracycline is given for 3 consecutive days as an IV push.
  2. Consolidation: even after complete remission, very few leukemic cells likely to remain undetected with current diagnostic techniques. If no further post-remission therapy is given, almost all patients will eventually relapse. Therefore, more therapy is necessary to eliminate non-detectable disease and prevent relapse — that is, to achieve a cure. The specific type of postremission therapy is individualized based on prognostic factors and general health:
     - For good-prognosis leukemias [t(8;21), and t(15;17)], patients will typically undergo an additional 3–5 courses of intensive chemotherapy
     - For patients at high risk of relapse (e.g. those with high-risk cytogenetics, underlying MDS, or therapy-related AML), allogeneic stem cell transplantation is usually recommended

Classification - French-American-British (FAB)

- MO - Undifferentiated
- M1 - Without maturation
- M2 - With granulocytic maturation
- **M3 - Acute promyelocytic**
- M4 - Granulocytic and monocytic maturation
- M5 - Monocytic
- M6 - Erythroleukemia
- M7 – Megakaryoblastic

M4 is NSE +ve
M5 is strongly +ve for NSE
M6 is PAS stain +ve

You are not normally expected to be able to differentiate the different subtypes of acute myeloid leukemia (AML) for the MRCP. An exception to this is acute promyelocytic leukemia (APML, the M3 subtype of AML). The importance of identifying APML lies in both the presentation (classically DIC) and management. APML is associated with the t(15:17) translocation which causes fusion of the PML and RAR-α genes.



Auer rod: an esoinophilic neede like inclusion in cytoplasm of blast cells is pathgenomic of AML

Diagnosis: The first clue is typically an abnormal CBC. While ↑ WBC is a common finding, and leukemic blasts are sometimes seen, AML can also present with isolated ↓ PLT, ↓ RBCs, or even ↓ WBC. While a presumptive diagnosis of AML can be made via examination of the peripheral blood smear when there are circulating leukemic blasts, a definitive diagnosis usually requires an adequate bone marrow aspiration and biopsy.

Poor prognostic features

- > 60 years
- > 20% blasts after first course of chemo
- Cytogenics: deletions of chromosome 5 or 7

Acute Promyelocytic Leukemia (APL) M3

ATRA (all-trans-retinoic acid): activates the RAR- α gene thus helps the WBCs to differentiate (i.e mature) but it will not eliminate the leukemia.

- Associated with t(15:17)
- Fusion of PML and RAR-α genes
- Presents younger than other types of AML (average = 25 years old)
- Chest infection, ↑WBC and DIC or thrombocytopenia often at presentation
- Good prognosis (curable with well-documented treatment protocols)
- Treated with the ATRA in addition to induction chemotherapy. Care must be taken to prevent DIC, complicating the treatment of APL when the promyelocytes release the contents of their granules into the peripheral circulation. APL is eminently.

Chronic Lymphocytic Leukemia (CLL)

Chronic Lymphocytic Leukemia (CLL) is caused by a **monoclonal proliferation** of well-differentiated **lymphocytes** which are almost always **B-cells** (99%)

Features

- Often none
- Constitutional: anorexia, weight loss
- Bleeding, infections
- Lymphadenopathy more marked than CML

Complications

- Hypogammaglobulinemia leading to recurrent **infections → most common cause of death**
- Warm autoimmune hemolytic anemia in 10-15% of patients
- Transformation to high-grade lymphoma (Richter's transformation)

Investigations

- Immunophenotyping (flow cytmetry)
- **Blood film: smear or smudge cells**

CLL - immunophenotyping is investigation of choice

Immunophenotyping will demonstrate the cells to be B-cells (CD19 positive). CD5 and CD23 are also characteristically positive in CLL

Indications for treatment

- Progressive marrow failure: the development or worsening of anemia and/or thrombocytopenia
- Massive (>10 cm) or progressive lymphadenopathy
- Massive (>6 cm) or progressive splenomegaly
- Progressive lymphocytosis: > 50% ↑ over 2 months or lymphocyte doubling time < 6 months
- Systemic symptoms: weight loss > 10% in previous 6 months, fever >38ºc for > 2 weeks, extreme fatigue, night sweats
- Autoimmune cytopenias e.g. ITP

Management

- None early on (when to start Rx is mentioned above)
- Chlorambucil to ↓ lymphocyte count
- Other options include fludarabine (because fludarabine causes profound lymphopenia, thus increases the risk of opportunistic infections significantly, prior to commensing fludarabine you must give co-trimoxazole or to use monthly nebulised pentamidine to prevent *Pneumocystis carinii* pneumonia)

Poor prognostic factors (median survival 3-5 years)

- ♂ Sex
- Age > 70 years
- Lymphocyte count > 50
- Prolymphocytes comprising > 10% of blood lymphocytes
- Lymphocyte doubling time < 12 months
- Raised LDH
- CD38 expression positive

Veno-Occlusive Disease (VOD) or Hepatic veno-occlusive disease. It is a complication of high-dose chemotherapy given before a bone marrow transplant (BMT). The name sinusoidal obstruction syndrome is now preferred if VOD happens as a result of chemotherapy or bone marrow transplantation. Treatment is primarily supportive.

Features:

- Fluid retention (weight gain, generalized edema, pleural effusion)
- Hepatomegaly
- ↑ Bilirubin (Jaundice)
- Usually complicated by multi-organ failure

Diagnosis:

- U/S abdomen helps in diagnosis
- Liver biopsy shows centrolobar necrosis

Lymphadenopathy is very uncommon in hairy cell leukemia

Hairy Cell Leukemia is a rare malignant proliferation disorder of B cells lymphocytes. It is more common in ♂s (4:1) and is usually classified as a sub-type of chronic lymphoid leukemia. Hairy cells are abnormal WBCs with hair-like projections of cytoplasm.

Features

- Pancytopenia (Monocytopenia is classical)
- Splenomegaly
- Skin vasculitis in 1/3 patients
- 'Dry tap' despite bone marrow hypercellularity (also seen in myelofibrrosis)
- Bone marrow biopsy migh show "fried egg appearance"
- Tartrate resistant acid phosphotase (TRAP) stain positive

Management

- Chemotherapy is first-line: cladribine, pentostatin
- Immunotherapy is second-line: rituximab, interferon-α
- Splenectomy sometimes required

Acute Lymphoblastic Leukaemia: causes damage and death by crowding out normal cells in the bone marrow, and by metastasizing. ALL is most common in childhood with a peak incidence at 2-5 years of age, and another peak in old age. The overall cure rate in children is ≈80%, and ≈45%-60% of adults have long-term disease-free survival. Acute → relatively short course of the disease (being fatal in as little as a few weeks if untreated)

Presentation: Initial symptoms are not specific to ALL, but worsen to the point that medical help is sought. The signs and symptoms of ALL are variable but follow from bone marrow infiltration and/or organ infiltration. t(12:21) is the most common translocation and portends a good prognosis. Philadelphia chromosome t(9:22) also has a bad prognosis. t(4:11) is the most common in children under 12 months and portends a poor prognosis.

Presentation:

- Generalized weakness and fatigue
- Anemia
- Frequent or unexplained fever and infections
- Weight loss and/or loss of appetite
- Excessive and unexplained bruising
- Bone pain, arthralgia.
- Dyspnea due to lung infiltration.
- Lymphandeopathy, hepatosplenomegaly.
- Pitting edema in the lower limbs and/or abdomen
- Petechiae due to thrombocytopenia

Diagnosis:

- Leukocytosis.
- Blast cells are seen on blood smear in 90% of cases
- Bone marrow biopsy is conclusive proof of ALL
- LP to detect CNS involvement.
- CXR: to look for mediastinal mass (common in ALL).

- U&E to look for Tumor Lysis Syndrome.
- Immunophenotyping, establish whether the "blast" cells origin is B or T lymphocytes
- DNA testing; different mutations reflect prognosis.

Terminal Deoxynucleotide Transferase (TdT) is present in 95% of ALL

Before treating with chemotherapy, if blast cell count is very ↑ (>100 x 10^9/L), the patient needs Leukapheresis to prevent sludgin of capillary beds, this can be life-saving

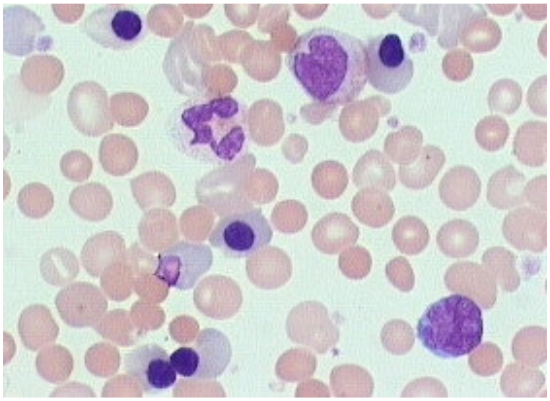
Good prognostic factors	Poor prognostic factors
• Common ALL • Pre-B phenotype • Low initial WBC • FAB L1 type	• FAB L3 type • T or B cell surface markers • Philadelphia translocation, t(9;22) • Age < 2 years or > 10 years • ♂ Sex. • CNS involvement • High initial WBC (e.g. > 100 * 10^9/l) • Non-Caucasian

Leukoerythroblastic Anemia

(left-shifted granulocytic series and nucleated red blood cells) with pancytopaenia. Also defined when there are immature cells (e.g myelocytes, and nucleated red blood cells) seen on the peripheral blood film.

Association:

- ↑ Bone marrow turnover e.g. in severe hemolytic anemia (in which case the reticulocyte count would be high).
- Myelofibrosis and Chronic Myeloid Leukaemia (where there would be splenomegaly, and the white cell and platelet count would usually be raised).
- Bone marrow invasion. Often in bone marrow invasion the invading malignancy will already have been diagnosed previously.
- Myeloma
- Polycythaemia Rubra Vera
- Osteopetrosis
- Tuberculous infiltration of the bone marrow
- Sarcoidosis



Hodgkin's Lymphoma is a malignant proliferation of lymphocytes characterized by the presence of the **Reed-Sternberg cell**. It has a bimodal age distributions being most common in the third and seventh decades. Hosgkin's lymphoma is associated with EBV. 25% of patients have a constitutional upset, (night sweats, weight loss, fever, pruritus and lethargy)

Ann-Arbor staging of Hodgkin's lymphoma

- I: single lymph node
- II: 2 or more lymph nodes/regions on same side of diaphragm
- III: nodes on both sides of diaphragm
- IV: spread beyond lymph nodes

Each stage may be subdivided into A or B

- A = no systemic symptoms other than pruritus
- B = weight loss > 10% in last 6 months, fever > 38c, night sweats (poor prognosis)

Other factors associated with a poor prognosis identified in a 1998 NEJM paper included:

- Age = 45 years
- Stage IV disease
- Hemoglobin < 10.5 g/dl
- Lymphocyte count < 600/µl or < 8%
- ♂
- Albumin < 40 g/l
- White blood count = 15,000/µl

Night sweats are a feature of non-Hodgkin's lymphoma

Types

Classical Hodgkin's lymphoma (excluding nodular lymphocyte predominant Hodgkin's lymphoma) can be subclassified into 4 pathologic subtypes based upon Reed-Sternberg cell morphology and the composition of the reactive cell infiltrate seen in the lymph node biopsy specimen (the cell composition around the Reed-Stenberg cell(s)).

Name	Description
Nodular sclerosing	Is **the most common subtype** and is composed of ***large*** tumor ***nodules*** showing scattered lacunar classical RS cells set in a background of reactive lymphocytes, eosinophils and plasma cells with varying degress of collagen fibrosis/***sclerosis***.
Mixed-cellularity subtype	Is a common subtype and is composed of numerous classic RS cells admixed with numerous inflammatory cells including lymphocytes, histiocytes, eosinophils, and plasma cells. Without sclerosis. This type is most often associated with EBV infection and may be confused with the early, so-called 'cellular' phase of nodular sclerosing CHL. **Good Prognosis**
Lymphocyte rich	Is a rare subtype, show many features which may cause diagnostic confusion with nodular lymphocyte predominant B-cell Non-Hodgkin's (B-NHL). **Best Prognosis**
Lymphocyte depleted	Is a **rare, the least subtype**, composed of large numbers of often pleomorphic RS cells with only few reactive lymphocytes which may easily be confused with diffuse large cell lymphoma. Many cases previously classified within this category would now be reclassified under anaplastic large cell lymphoma. **Worse Prognosis**
Unspecified	

Nodular lymphocyte predominant Hodgkin's lymphoma expresses CD20, and is not currently

considered a form of classical Hodgkin's → Remember, Rituximab is anti-CD20.

Diagnosis:

- Hodgkin results in patchy bone marrow infiltration, an isolated bone marrow biopsy may yield non-specific results.
- Bone marrow biopsy is more useful for staging of advanced disease.
- Lymph node biopsy would be more likely to be positive, Reed-Sternberg cell is evident on microscopy

Management:

- Early stage **(IA or IIA)** are effectively treated with **radiation therapy AND chemotherapy**. The choice of treatment depends on the age, sex, bulk and the histological subtype of the disease.
- Later disease **(III, IVA, or IVB)** are treated with **combination chemotherapy alone**.
- **Large mass in the chest** (regardless of stage) are usually treated with **combined chemotherapy and radiation therap**. Chemo includes: Doxorubicin, Bleomycin, Vincristine, Cyclophosphamide and other cytotoxic drugs.

Non-Hodgkin's Lymphomas: are a diverse group of lymphomas that include any kind of lymphoma except Hodgkin's lymphomas. Types of NHL vary significantly in their severity, from indolent to very aggressive. Low-grade lymphoma is predominantly a disease of older people. Most non-Hodgkin's lymphomas are of B cell phenotype, though T cell tumours are increasingly being recognized.

Presentation:

- Most present with advanced disease, bone marrow infiltration being almost invariable.
- Burkitt's lymphoma is a high-grade lymphoma, which was first described in children in West Africa who presented with a jaw tumour, extra-nodal abdominal involvement and ovarian tumours.
- Extra-nodal presentation is more common than Hodgkin's disease.
- Renal impairment in non-Hodgkin's lymphomas usually occurs as a consequence of ureteric obstruction secondary to intra-abdominal or pelvic lymph node enlargement.
- Anaemia, an elevated white cell count and/or thrombocytopaenia are suggestive of bone marrow infiltration.

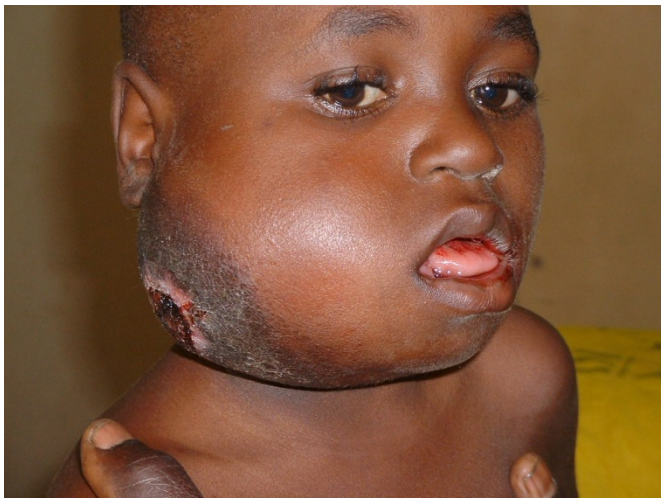
Management:

- Lymph node biopsy is sufficient for a definitive diagnosis.
- It is essential for modern classification to submit the lymphoid tissue for immuno-phenotyping and cytogenetic/molecular analysis.
- High-grade lymphomas are responsive to chemotherapy and potentially curable,
- Low-grade lymphomas are incurable with conventional therapy.
- Chemotherapy is the mainstay of treatment in most cases.

Burkitt's lymphoma is a common cause of tumor lysis syndrome

Burkitt's Lymphoma is a high-grade B-cell neoplasm (NHL). There are two major forms:

- Endemic (African) form: typically involves maxilla or mandible
- Sporadic form: abdominal (**ileo-caecal**) tumors are **the most common form**. More common in patients with HIV



Burkitt's lymphoma is associated with the c-myc gene translocation, usually t(8:14). The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form but the link to sporadic Burkitt's is less clear

Management is with chemotherapy. This tends to produce a rapid response which may cause 'tumor lysis syndrome'.

Tumor Lysis Syndrome (TLS): This occurs after the initiation of a chemotherapeutic. TLS tends to occur in patients with bulky, rapidly proliferating, treatment-responsive tumors

Association:

- Acute leukemia
- High-grade non-Hodgkin's lymphomas.
- Pre-treatment ↑ LDH (levels of LDH correspond with tumor bulk)

Manifestation: rapid development (48-72 hours after initiation) of

- ↑ kalemia (1st life-threatening abnormality)
- ↑ uricemia
- ↑ phosphatemia
- ↓ calcemia
- Acute renal failure.

Management:

- Prevention is with good hydration before starting chemotherapy.
- ↑ uricemia → urine alkalinisation and allopurinol
- Osmotic diuretics are **NOT** first line therapy and may contribute to the precipitation of uric acid in the renal tubules.
- Dietary modifications include restricting dietary potassium.
- **Further chemotherapy should be withheld until the patient has fully recovered**

Hematological malignancies: genetics

Common Chromosomal Translocation and Associated Hematological Malignancy	
t(9;22) Philadelphia chromosome	• Present in **> 95% of patients with CML** • This results in part of the Abelson (ABL) proto-oncogene being moved to the BCR gene on chromosome 22 • The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal • **Poor prognostic indicator in ALL and AML**
t(15;17)	• Seen in acute promyelocytic leukemia (M3) • Fusion of PML and RAR-α genes
t(8;14)	• Seen in Burkitt's lymphoma • MYC oncogene is translocated to an immunoglobulin gene
t(11;14)	• Mantle cell lymphoma • Deregulation of the cyclin D1 (BCL-1) gene

Hematological Malignancies: Infections

Viruses

- EBV: Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma
- HTLV-1 (Human T-lymphotropic virus Type I): Adult T-cell leukemia/lymphoma
- HIV-1: High-grade B-cell lymphoma

Bacteria

- *Helicobacter pylori*: gastric lymphoma (MALT)

Protozoa

- Malaria: Burkitt's lymphoma

Notes on Bone Marrow Transplant:

- Stem cell transplants from unrelated or haploidentical donors are not used in first complete remission in most adult hematological malignancies due to the high treatment related mortality/morbidity: they are reserved for first relapse/second complete remission.
- Stem cell transplants from matched sibling donors are used as first line therapy in certain circumstances, including chronic myeloid leukaemia.
- Irradiated blood is required in patients receiving a bone marrow transplant, patients with previous purine analogue exposure and a diagnosis of Hodgkin's disease.
- Cytomegalovirus (CMV)-negative blood should be used in patients who may need a bone marrow transplant in the future (since carriage of CMV increases transplant mortality).
- Imatinib is targeted to inhibit the novel tyrosine kinase that is formed from the genetic translocation between chromosomes 9 and 22, which is the hallmark of chronic myeloid leukaemia. Imatinib mesylate used as first line therapy brings about complete cytogenetic remissions in 76% of patients, with some patients becoming negative by polymerase chain reaction for the 9:22 translocation. It is not however thought to be curative, and young patients with a sibling donor are still referred for transplantation.

In summary, in the absence of siblings, imatinib to induce remission is the initial therapy of choice in patient with no siblings. If patient had siblings then related stem cell transplant may be considered.

Causes of Eosinophilia may be divided into pulmonary, infective and other

Pulmonary causes	Infective causes	Other causes
• Asthma • Allergic bronchopulmonary aspergillosis • Churg-strauss syndrome • Loffler's syndrome • Tropical pulmonary eosinophilia • Eosinophilic pneumonia • Hypereosinophilic syndrome	• Schistosomiasis • Nematodes: Toxocara, Ascaris, Strongyloides • Cestodes: Echinococcus	• Drugs: sulfasalazine, nitrofurantoin • Psoriasis/eczema • Eosinophilic leukemia (very rare)

Diseases that feature eosinophilia:

- Hypereosinophilic syndrome
- Parasitic infections (intestinal helminthiasis)
- Allergic disorders (including eosinophilic esophagitis)
- Some drug reactions, e.g. DRESS syndrome
- Cholesterol embolization
- Some forms of chronic myeloid leukemia
- Hodgkin's lymphoma
- Gleich's syndrome
- Addison's disease
- Clonorchis sinensis, a type of flatworm
- Eosinophilia-myalgia syndrome caused by contaminated tryptophan supplements
- Job's Syndrome caused by ↑ levels of Immunoglobulin E
- A form of Collitis, eosinophilic collitis

A useful mnemonic for remembering causes of eosinophilia is NAACCP: Neoplasia, Addison Disease, Allergy/Asthma, Collagen Vascular diseases, Cholesterol emboli, and parasites.

Hyper Eesinophilic syndrome: rare unknown cause disease, occurring most commonly in ♂ in the 30-40-year-age group with persistent and markedly raised peripheral blood eosinophil count.

Association:

- Lung involvement may occur
- Cardiovascular involvement with fibrosis and restrictive cardiomyopathy, which may lead to mural thrombus formation and considerable morbidity and mortality.
- Angioedema or urticaria.

Treatment: is with high dose corticosteroids (e.g. prednisolone 50mg which leads to a response in around 50% of cases). Steroid sparing agents such as cyclophosphamide or azathioprine may also be of some value.

Condition	Prothrombin time	Partial thromboplastin time	Bleeding time	Notes
Vit. K deficiency	prolonged	prolonged	unaffected	1 normal
DIC	prolonged	prolonged	prolonged	All affected
Hemophilia	unaffected	prolonged	unaffected	1 affected

Factor	PT	APTT
VII	↑	≡
II – V – X	↑	↑
VIII – IX – XI – XII	≡	↑

- Factor VII deficiency is very rare, is inherited in an autosomal recessive fashion, and tends to cause a mild/moderate bleeding disorder, although the phenotype does vary. Treatment is by factor replacement with plasma-derived products or using recombinant activated factor VII.
- When an abnormality is detected in the PT/APTT the studies are repeated with a 50:50 mix of test and normal plasma: straightforward factor deficiencies will correct with mixing, but inhibitors (most commonly lupus anti-coagulant) do not correct. It should be noted however that the results of PT mixing studies in patients on warfarin are consistent with factor deficiencies, because warfarin acts as an anti-coagulant by decreasing the activity of factors II, VII, IX, and X.

Acquired Factor VIII Deficiency results from the development of inhibitors against factor VIII coagulation factor. It occurs mainly in elderly.

Association:
- Malignancy
- Psoriasis
- Pemphigus
- Drugs: cephalosporins, penicillins

Diagnosis:
- Bleeding tendencies
- APTT: is prolonged (intrinsic pathway).
- APTT doesn't correct/will only correct slightly with the adding of normal plasma.
- Bethesda titre can quantify the inhibitor. There is a 20% mortality rate from acquired factor VIII deficiency.

Treatment:
- Replacement of factor VIII is usually ineffective as the inhibitor has rapid activity.
- Bleeding can be treated with recombinant activated factor VII or Factor Eight Bypassing Agent (FEIBA), but the latter is a pooled donor product and is pro-thrombotic, causing myocardial infarctions and DIC in a subset of patients.
- rFVIIa has been successfully used in patients with acquired hemophilia. It binds to the surface of activated platelets, where it supports thrombin generation and bypasses the need for FVIII.
- Definitive removal of the auto-antibody: immunosuppression is successful in at least half of patients, but carries significant morbidity and mortality in the elderly

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Activated protein C resistance (Factor V Leiden) is the most common inherited thrombophilia

It is due to a mutation in the Factor V Leiden gene. Heterozygotes have a 5-fold risk of venous thrombosis whilst homozygotes have a 50-fold ↑ risk. Any white pt aged <45 with thrombotic event should make you think of factor V Leiden mutation.

Von Willebrand's disease is the most common inherited bleeding disorder

Hemophilia A	**X-linked** genetic disorder involving a lack of functional clotting ***Factor VIII*** and represents 90% of Hemophilia cases
Hemophilia B	**X-linked** genetic disorder involving a lack of functional clotting ***Factor IX*** (Christmas disease) It is more severe but less common than Hemophilia A
Hemophilia C	Autosomal genetic (***not* X-linked**) lack of functional clotting ***Factor XI***. It is not completely recessive: heterozygous individuals also show ↑ bleeding

Acquired Hemophilia: is associated with anti-factor VIII IgG antibodies and is idiopathic in the majority of cases.

Association:

- Autoimmune diseases: (Rheumatoid Arthritis or IBD)
- Drugs such as phenytoin.

Management:

- Where there are ↓ anti-factor VIII antibodies, factor VIII replacement may be all that is required.
- Where bleeding is a serious problem then immunosupression with corticosteroids +/- steroid sparing agents such as cyclosporine may be required.

Thrombophilia: causes

Inherited	Acquired
• Activated protein C resistance (factor V Leiden) • Antithrombin III deficiency • Protein C deficiency • Protein S deficiency	• Antiphospholipid syndrome • The Pill (COCP)

Heparin works by binding to antithrombin III, enhancing its anticoagulant effect by inhibiting the formation of thrombin and other clotting factors. Patients with antithrombin III deficiency may therefore by resistant to heparin treatment

Antithrombin III Deficiency is an inherited cause of thrombophilia occurring in approximately 1:2,000 of the population. Inheritance is autosomal dominant

Antithrombin III inhibits several clotting factors, primarily thrombin, factor X and factor IX. It mediates the effects of heparin

Antithrombin III deficiency comprises a heterogeneous group of disorders, with some patients having a deficiency of normal antithrombin III whilst others produce abnormal antithrombin III

Features

- Recurrent venous thromboses
- Arterial thromboses do occur but is uncommon

Management

- Thromboembolic events are treated with lifelong warfarinisation
- Heparinisation during pregnancy*
- Antithrombin III concentrates (often using during surgery or childbirth)

*as patients with antithrombin III deficiency have a degree of resistance to heparin anti-Xa levels should be monitored carefully to ensure adequate anticoagulation

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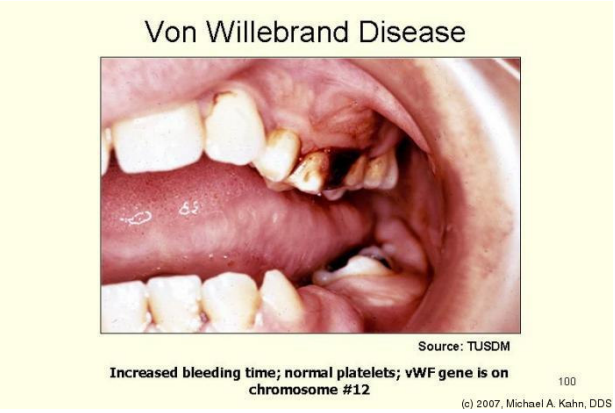
Von Willebrand's disease is the **most common inherited bleeding disorder**. The majority of cases are inherited in an autosomal dominant fashion* and characteristically behaves like a platelet disorder i.e. **epistaxis and menorrhagia are common** whilst hemoarthroses and muscle hematomas are rare.

Role of von Willebrand factor

- Large glycoprotein which forms massive multimers up to 1,000,000 Da in size
- Promotes platelet adhesion to damaged endothelium
- Carrier molecule for factor VIII



Types

- type 1: partial reduction in vWF (80% of patients)
- type 2: abnormal form of vWF
- type 3: total lack of vWF (autosomal recessive) most severe

NEW TEST
PFA-100 has > 95% sensitivity to diagnose VWD

Presentation:

- Petechial skin
- **Slightly elevated APTT**
- ↓ factor VIII activity

Investigation

- Prolonged bleeding time
- APTT may be prolonged
- Factor VIII levels may be moderately ↓
- Defective platelet aggregation with ristocetin

Management

- Tranexamic acid for mild bleeding
- Desmopressin (DDAVP): raises levels of vWF by inducing release of vWF from Weibel-Palade bodies in endothelial cells. Used as prohyplaxis prior to procedures.
- Factor VIII concentrate

Thrombocytopenia

Causes of severe thrombocytopenia

- ITP
- TTP
- DIC
- Hematological malignancy

Causes of moderate thrombocytopenia

- Heparin induced thrombocytopenia (HIT)
- **Drug-induced (e.g. quinine, diuretics, sulphonamides, aspirin, thiazides)**
- Alcohol and Vitamin B12 deficiency
- Liver disease
- Hypersplenism
- Viral infection (EBV, HIV, hepatitis)
- Pregnancy
- SLE/antiphospholipid syndrome

Idiopathic thrombocytopenic purpura (ITP) is an immune mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb-IIIa or Ib complex. ♀:♂=2.6:1. Common cause of death is bleeding (mainly intracranial).

Investigations

- Antiplatelet autoantibodies (usually **IgG**)
- Bone marrow aspiration shows megakaryocytes in the marrow. This should be carried out prior to the commencement of steroids in order to rule out leukemia

Management

- Oral prednisolone (80% of patients respond)
- Splenectomy if platelets < 30 after 3 months of steroid therapy
- IV immunoglobulins
- Immunosuppressive drugs e.g. Cyclophosphamide

ITP can be divided into acute and chronic forms:

- Acute ITP
    - More commonly seen in children
    - Equal sex incidence
    - May follow an infection or vaccination
    - Usually runs a self-limiting course over 1-2 weeks

- Chronic ITP
    - More common in young/middle-aged women
    - Tends to run a relapsing-remitting course

Evan's syndrome

- ITP in association with autoimmune hemolytic anemia (AIHA)

Livedo reticularis is not commonly seen in TTP. It occurs more commonly in conditions such as antiphospholipid syndrome and cholesterol embolism

HUS or TTP? Neuro signs and purpura point towards TTP

The combination of neurological features, renal failure, pyrexia and thrombocytopenia point towards a diagnosis of TTP

Thrombotic thrombocytopenic purpura

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- Abnormally large and sticky multimers of vWF cause platelets to clump within vessels
- In TTP there is a deficiency of caspase which breakdowns large multimers of vWF.
- Overlaps with hemolytic uraemic syndrome (HUS)

Features

- Rare, typically adult ♀
- **Fever**
- **Fluctuating neuro signs (microemboli)**
- Microangiopathic hemolytic **anemia**
- **Thrombocytopenia**
- **Renal failure**

Causes

- Post-infection e.g. Urinary, gastrointestinal
- Pregnancy
- Drugs: cyclosporin, oral contraceptive pill, penicillin, clopidogrel, aciclovir
- Tumors
- SLE
- HIV

The management of thrombotic thrombocytopenic purpura involves steroids and immunosuppressants. Plasma exchange is the treatment of choice

Management

- No antibiotics - may worsen outcome
- Plasma exchange is the treatment of choice
- Steroids, immunosuppressants
- Vincristine

Drug causes of pancytopenia

- Cytotoxics
- Antibiotics: trimethoprim, chloramphenicol
- Anti-rheumatoid: gold, penicillamine
- Carbimazole*
- Anti-epileptics: carbamazepine
- Sulphonylureas: tolbutamide

*causes both agranulocytosis and pancytopenia

Heparin Induced Thrombocytopenia (HIT): is a severe immune-mediated drug reaction that can occur in patients receiving unfractionated heparin (at full therapeutic doses and low prophylactic doses, including the minute amounts in heparin flushes and on heparin-coated catheters) and those receiving low-molecular weight heparin (LMWH). Antibodies usually develop after a patient has been on heparin for five or more days, but may develop sooner if there has been previous heparin exposure.

Presentation: Despite thrombocytopenia, bleeding is rare. HIT is strongly associated with thrombosis. Thromboembolic complications can be venous, arterial, or both, and include:

- DVT
- Pulmonary embolism
- Myocardial infarction
- Thrombotic stroke
- Occlusion of limb arteries.

Types:

- Type I**:** usually occurs 48 to 72 hours post commensing heparing and PLT rarely < 100. PLT returns to normal over 4 days and there is no ↑ risk of thromboembolism
- Type II**:** much rarer and usually occurs 5 to 10 days after starting heparin, PLT usually <100, patients are at ↑ risk of thromboembolic events. Heparin products should be stopped and the patient commenced on alternative medication

Management: should be started on suspicion, before confirming the diagnosis

- Stop all forms of Heparin
- Start alternative anticoagulant which do not cross-react with HIT antibodies, such as:
  - Danaparoid
  - Lepirudin
  - Argatroban.
- Oral anticoagulation with warfarin should **NOT** be initiated for longer-term protection from further events until substantial platelet count recovery has occurred. HIT patients who are switched to warfarin alone after the discontinuation of heparin may paradoxically have worsening thrombosis and develop venous limb gangrene and skin necrosis.

Diagnosis: is clinical:

- Thrombocytopenia: PLT < 100 or <50% from the patient's baseline
- The exclusion of other causes of thrombocytopenia
- The resolution of thrombocytopenia after cessation of heparin.
- Supportive lab tests: HIT antibodies can be demonstrated in vitro by functional tests (are more specific) and immunoassays. Functional tests; measure platelet activity in the presence of the patient's serum and heparin include:
  - Heparin Induced Platelet Aggregation (HIPA)
  - Serotonin Release Assay (SRA)

Blood films: Typical Pictures

Hyposplenism e.g. post-splenectomy

- Target cells
- Howell-Jolly bodies
- Cabot's rings
- Siderotic granules
- Acanthocytes
- Schizocytes

Iron-deficiency anemia

- Target cells
- 'Pencil' poikilocytes
- If combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

Features:

- koilonychia
- atrophic glossitis
- post-cricoid webs
- angular stomatitis

G6PD Deficiency

- Heinz bodies

Myelofibrosis

- 'Tear-drop' poikilocytes

Intravascular hemolysis

- Schistocytes

Megaloblastic anemia

- Hypersegmented neutrophils

Blood Film	Condition
Smudge or smear cells	**CLL**
Lymphocytes with polar villi	**Splenic lymphoma with villous lymphocytes**
Lymphocytes (mature) with cleaved nuclei	**Follicular lymphoma**
Lymphocytes (immature) with prominent nuclei	**ALL**

Stains & Reagents used in Hematology:

Tartrate-Resistant Acid Phosphatase TRAP	Always +ve in hairy cell leukaemia
Sudan black B stain and myeloperoxidase	acute myeloblastic leukaemia
Terminal Deoxynucleotidyl Transferase Stain (TDT)	acute lymphoblastic leukaemia
Leukocyte Alkaline Phosphatase (LAP)	↑ in polycythemia RV and myelofibrosis ↓ in chronic myeloid leukaemia

Hereditary Hemorrhagic Telangiectasia:

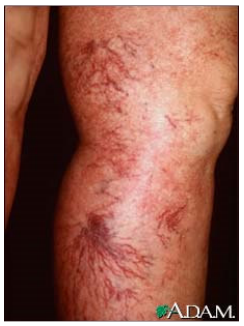
Also known as Osler-Weber-Rendu syndrome, hereditary hemorrhagic telangiectasia is an autosomal dominant condition characterized by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. 20 % of cases occur spontaneously without prior family history.

Types: 5 are identified HHT1 to HHT4 and JPHT (HHT and juvenile polyposis)

- HHT1: chromosome 9, associated with ↑ AVM (cerebral and pulmonary)
- HHT2: chromosome 12.

Features

- Epistaxis
- Telangiectasia develop ob skin, mucous membranes and internal organs
- Associated with pulmonary and other AV malformations in 10%
- May present as iron-deficiency anemia secondary to bleeding in the GI tract or nasal mucosa



Waldenstrom's Macroglobulinemia

is an uncommon condition seen in older men. It is a lymphoplasmacytoid malignancy characterized by the **secretion of a monoclonal IgM paraprotein**

Features:

- Monoclonal IgM paraproteinemia
- Systemic upset: weight loss, lethargy
- Hyperviscosity syndrome e.g. Visual disturbance
- Hepatosplenomegaly
- Lymphadenopathy
- Cryoglobulinemia e.g. Raynaud's
- ↑ ESR

Management:

- Alkylating agents
- Young patient may benefit from doxorubicin.
- Treatment includes the monoclonal antibody rituximab, sometimes in combination with chemotherapeutic drugs such as chlorambucil, cyclophosphamide, or Vincristine or with thalidomide.
- Corticosteroids, such as Prednisone, may also be used in combination.
- Plasmapheresis can be used to treat the hyperviscosity (it does not address the underlying disease)

Monoclonal Gammopathy of Undetermined Significance (MGUS)

also known as benign paraproteinemia and monoclonal gammopathy) is a common condition that causes paraproteinemia and is often mistaken for myeloma. Differentiating features are listed below. Around 10% of patients eventually develop myeloma at 5 years, with 50% at 15 years

One of the key differentiating features between (MGUS) and myeloma is the absence of complications such as immune paresis, hypercalcemia and bone pain

Features

- Usually asymptomatic
- No bone pain or ↑ risk of infections
- Around 10-30% of patients have a demyelinating neuropathy
- M protein level < 30gm/l
- No end-organ damage.

Differentiating features from myeloma

- Normal immune function
- Normal β-2 microglobulin levels
- Lower level of paraproteinemia than myeloma (e.g. < 30g/l IgG, or < 20g/l IgA)
- Stable level of paraproteinemia
- No clinical features of myeloma (e.g. Lytic lesions on x-rays or renal disease)

Diagnostic Criteria:

- Serum paraprotein <30 g/L AND
- Clonal plasma cells <10% on bone marrow biopsy AND
- NO myeloma-related organ or tissue impairment

Methemoglobinemia

Methemoglobinemia describes hemoglobin which has been oxidised from Fe^{++} (Ferrous) to Fe^{+++}. This is normally regulated by NADH methemoglobin reductase, which transfers electrons from NADH to methemoglobin resulting in the reduction of methemoglobin to hemoglobin. There is tissue hypoxia as Fe3+ cannot bind oxygen, and hence the oxidation dissociation curve is moved to the left

Methemoglobinemia = oxidation of Fe2+ in hemoglobin to Fe3+

Congenital causes

- Hemoglobin chain variants: HbM, HbH
- NADH methemoglobin reductase deficiency

Acquired causes

- Drugs: sulphonamides, nitrates, dapsone, sodium nitroprusside, primaquine
- Chemicals: aniline dyes

Features

- 'Chocolate' cyanosis
- Dyspnea, anxiety, headache
- Severe: acidosis, arrhythmias, seizures, coma
- **Normal PO_2 but ↓ oxygen saturation**

Management

- NADH - methemoglobinemia reductase deficiency: ascorbic acid
- IV methylene blue if acquired

Fanconi's Anemia:

- Autosomal recessive
- Aplastic anemia
- ↑ risk of AML
- Neurological manifestation
- Skeletal abnormalities
- Skin pigmentation (café-au-lait spots)

Screening for hemochromatosis
- General population: transferrin saturation > ferritin
- Family members: HFE genetic testing

Hemochromatosis is the most prevalent genetic condition in Caucasian population with a carrier rate of 1 in 10 and is present in about 1 in 200-400 people. Cystic fibrosis (CF) has a carrier rate of 1 in 25 and is present in about 1 in 2,500 births. **CF is often quoted as being the most common lethal inherited condition in Caucasians**

Hemochromatosis is an autosomal recessive disorder of iron absorption and metabolism resulting in iron accumulation. It is caused by inheritance of mutations in the HFE gene on both copies of chromosome 6*. The British Committee for Standards in Hematology (BCSH) published guidelines for the investigation and management of hemochromatosis in 2000

There is continued debate about the best investigation to screen for hemochromatosis. The 2000 BCSH guidelines suggest:
- General population: transferrin saturation is considered the most useful marker. Ferritin should also be measured but is not usually abnormal in the early stages of iron accumulation
- Testing family members: genetic testing for HFE mutation
- These guidelines may change as HFE gene analysis become less expensive

Diagnostic tests
- Molecular genetic testing for the C282Y and H63D mutations
- Liver biopsy: Perl's stain

Typical iron study profile in patient with hemochromatosis
- Transferrin saturation > 55% in men or > 50% in women
- Raised ferritin (e.g. > 500 ug/l) and iron
- Low TIBC

Monitoring adequacy of venesection
- BSCH recommend 'transferrin saturation should be kept below 50% and the serum ferritin concentration below 50 ug/l'

*there are rare cases of families with classic features of genetic hemochromatosis but no mutation in the HFE gene

It is often asymptomatic in early disease and initial symptoms often non-specific e.g. lethargy and arthralgia

Presenting features
- Early symptoms include fatigue, erectile dysfunction and arthralgia (often of the hands)
- 'Bronze' skin pigmentation
- Diabetes Mellitus
- Liver: stigmata of chronic liver disease, hepatomegaly, cirrhosis, hepatocellular deposition.
- Cardiac failure (2nd to dilated cardiomyopathy)
- Hypogonadism (2nd to cirrhosis and pituitary dysfunction - hypogonadotrophic hypogonadism)
- Arthritis (especially of the hands)

Joint x-rays characteristically show chondrocalcinosis

Questions have previously been asked regarding which features are reversible with treatment:

Reversible complications	Irreversible complications
• Cardiomyopathy • Skin pigmentation	• Liver cirrhosis** • Diabetes mellitus • Hypogonadotrophic hypogonadism • Arthropathy

**whilst elevated liver function tests and hepatomegaly may be reversible, cirrhosis is not

Splenectomy: Following a splenectomy patients are particularly at risk from pneumococcus, Hemophilus, meningococcus and Capnocytophaga canimorsus (usually from dog bite) infections

Vaccination

- If elective, should be done 2 weeks prior to operation
- Pneumococcal, HIB, meningitis A & C and annual influenza vaccination

Antibiotic prophylaxis

- Penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life

Hyposplenism:

Causes

- Splenectomy
- Sickle-cell
- **Coeliac disease, dermatitis herpetiformis (HLA DR3)**
- **Graves' disease**
- **SLE**
- **Amyloid**

Features

- Howell-Jolly bodies
- Siderocytes

Aplastic Anemia: management:

Supportive

- Blood products
- Prevention and treatment of infection

Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG)

- Prepared in animals (e.g. Rabbits or horses) by injecting human lymphocytes
- Is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given
- Immunosuppression using agents such as Cyclosporin may also be given

Stem cell transplantation

- Allogeneic transplants have a success rate of up to 80%

It is important in a patient who is also deficient in both vitamin B12 and folic acid to treat the B12 deficiency first to avoid precipitating subacute combined degeneration of the cord

Macrocytic anemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

Megaloblastic causes:	Normoblastic causes:
• Vitamin B12 deficiency • Folate deficiency • Cytotoxics e.g. Hydroxyurea	• Alcohol • Liver disease • Hypothyroidism • Pregnancy • Reticulocytosis e.g. Hemolysis • Aplastic anemia • Myelodysplasia • Drugs: cytotoxics

Thalassemia: is a hemoglobinopathy resulting from defective synthesis of globin chains required for hemoglobin synthesis. Each copy of **chromosome 16** has two genes for the **alpha globin** subunit (four in total), and each copy of **chromosome 11** has one gene for the **beta subunit** (two in total). Adult hemoglobin HbA(α2β2), second adult hemoglobin HbA2(α2δ2), fetal hemoglobin HbF(α2γ2).

(α) Thalassemias is due to a deficiency of α chain in hemoglobin

- 2 separate α-globulin genes are located on each **chromosome 16**
- Clinical severity depends on the number of α chains present
- If 1 or 2 α chains are absent then the blood picture would be hypochromic and microcytic, but the Hb level would be typically normal
- Loss of 3 α chains results in a hypochromic microcytic anemia with splenomegaly. This is known as HbH disease
- If all 4 α chains absent (i.e. homozygote) then death in utero (hydrops fetalis, Bart's hydrops)
    - 1 gene deletion: silent carrier
    - 2 gene deletion: α-thalassaemia trait (microcytosis, +/- anemia, decreased HbA2)
    - 3 gene deletion: hemoglobin H disease (β4)-moderate anemia, splenomegaly
    - 4 gene deletion: Bart's hemoglobin(γ4) - hydrops fetalis

(β) Thalassemias

Beta thalassemias are due to mutations in the HbB gene on chromosome 11, also inherited in an autosomal-recessive fashion. The severity of the disease depends on the nature of the mutation. Mutations are characterized as (βo or β thalassemia major): if they prevent any formation of β chains, which is the most severe form of β thalassemia. (β+ or β thalassemia intermedia) if they allow some β chain formation to occur. In either case there is a relative excess of α chains, but these do not form tetramers: rather, they bind to the red blood cell membranes, producing membrane damage, and at high concentrations they form toxic aggregates.

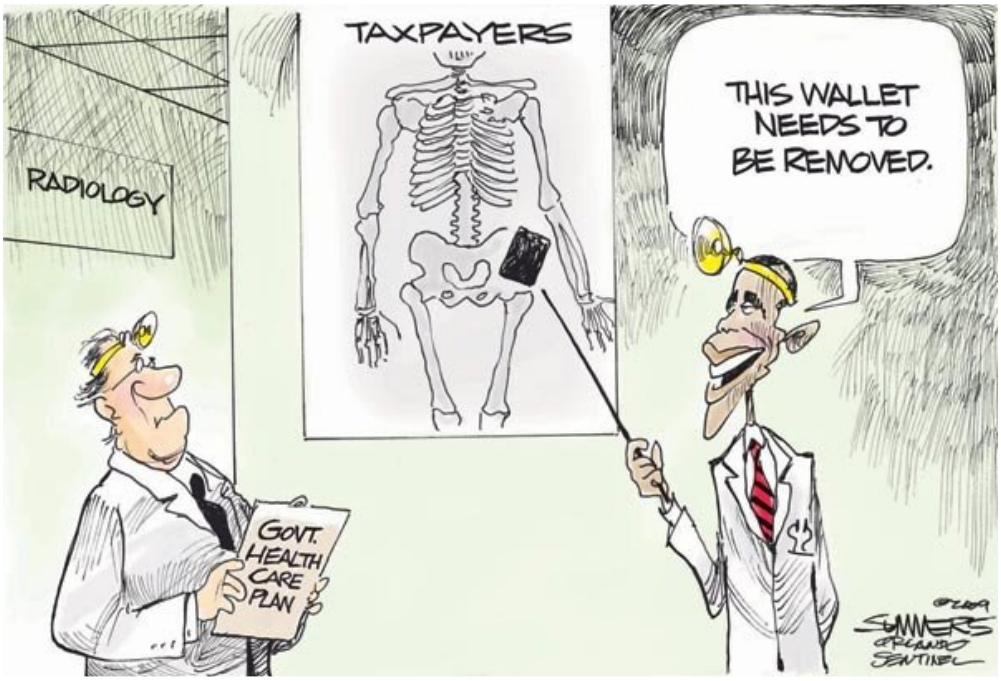
- 1 gene deletion: β-thalassaemia minor (mild anaemia, microcytosis, elevated HbA2)
- 2 gene deletion: β -thalassaemia major (anaemia when HbF tries to convert to HbA during first year of life, extramedullary hemopoiesis with hepatosplenomegaly and bone marrow expansion, 'hair on end' appearance of bone).

Delta (δ) Thalassemia

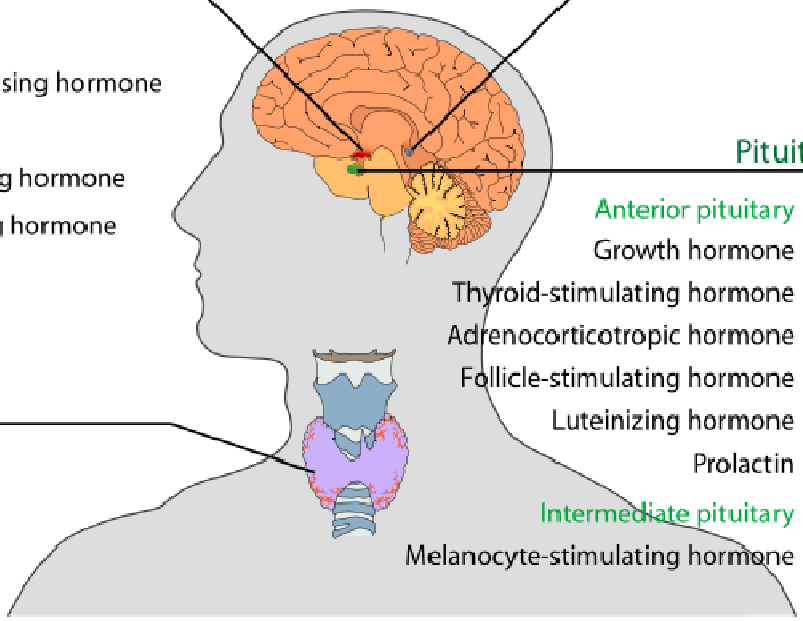
As well as alpha and beta chains being present in hemoglobin about 3% of adult hemoglobin is made of alpha and delta chains. Just as with beta thalassemia, mutations can occur which affect the ability of this gene to produce delta chains.

Thalassemia can co-exist with other hemoglobinopathies. The most common of these are:

- **Hemoglobin E/thalassemia**: common in Cambodia, Thailand, and parts of India; clinically similar to β thalassemia major or thalassemia intermedia.
- **Hemoglobin S/thalassemia**, common in African and Mediterranean populations; clinically similar to sickle cell anemia, with the additional feature of splenomegaly
- **Hemoglobin C/thalassemia**: common in Mediterranean and African populations, hemoglobin C/βo thalassemia causes a moderately severe hemolytic anemia with splenomegaly; hemoglobin C/β+ thalassemia produce a milder disease.


RADIOLOGY
TAXPAYERS
THIS WALLET NEEDS TO BE REMOVED.
GOVT. HEALTH CARE PLAN
SUMMERS
ORLANDO SENTINEL

ENDOCRINOLOGY



Anti-TSH receptor stimulating autoantibodies (often referred to as Thyroid Stimulating Immunoglobulins) are almost diagnostic of Graves' disease, the most common cause of thyrotoxicosis in the UK

It is well documented that radioiodine therapy can precipitate thyroid eye disease but a majority of patients will eventually require thyroxine replacement due to hypothyroidism

Graves' Disease:

Features seen in Graves' but not in other causes of thyrotoxicosis

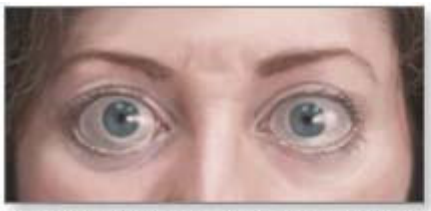
- Eye signs: exophthalmos, ophthalmoplegia
- Pretibial myxedema
- Thyroid acropachy

Autoantibodies

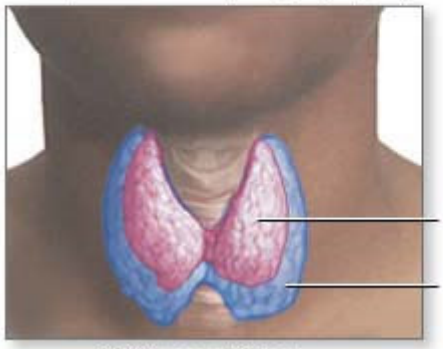
- Anti-TSH receptor stimulating antibodies (90%)
- Anti-thyroid peroxidase antibodies (50%)

Labs:

- Low TSH (0.5 – 5.5)
- Elevated Total T4 (9-22)



Exophthalmos (bulging eyes)



Diffuse goiter

Graves' disease is a common cause of hyperthyroidism, an over-production of thyroid hormone, which causes enlargement of the thyroid and other symptoms such as exophthalmos, heat intolerance and anxiety

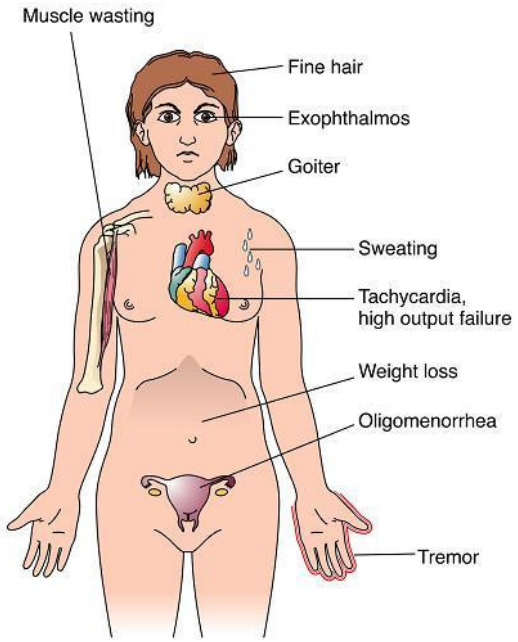
ADAM.

Management

Despite many trials there is no clear guidance on the optimal management of Graves' disease. Treatment options include titration of anti-thyroid drugs (ATDs, for example carbimazole), block-and-replace regimes, radioiodine treatment and surgery. Propranolol is often given initially to block adrenergic effects

ATD titration

- Carbimazole is started at 40mg and ↓ gradually to maintain euthyroidism
- Typically continued for 12-18 months
- Patients following an ATD titration regime have been shown to suffer fewer side-effects than those on a block-and-replace regime



Block-and-Replace

- Carbimazole is started at 40mg
- Thyroxine is added when the patient is euthyroid
- Treatment typically lasts for 6-9 months

The major complication of carbimazole therapy is agranulocytosis (pancytopenia)

Radioiodine Treatment

- Contraindications include pregnancy (should be avoided for 4-6 months following treatment) and age < 16 years. Thyroid eye disease is a relative contraindication, as it may worsen the condition
- The proportion of patients who become hypothyroid depends on the dose given, but as a rule the majority of patient will require thyroxine supplementation after 5 years, so **hypothyroidism is the most common side effect of radioiodine Rx.**

Thyrotoxicosis

Causes

- Graves' disease
- Toxic nodule goitres
- Subacute (de Quervain's) thyroiditis
- Post-partum thyroiditis
- Acute phase of Hashimoto's thyroiditis (later results in hypothyroidism)
- Toxic adenoma (Plummer's disease)
- Amiodarone therapy

Investigation

- TSH down, T4 and T3 up
- Thyroid autoantibodies
- Other investigations are not routinely done but includes isotope scanning

TSH is used to assess the response of pt to carbimazole for treating Grave's

Toxic Multinodular Goitre describes a thyroid gland that contains a number of autonomously functioning thyroid nodules that secrete excess thyroid hormones. Nuclear scintigraphy reveals patchy uptake. The treatment of choice is radioiodine therapy

Toxic adenoma (Plummer's disease) Management:

- Radioiodine
- Subtotal thyroidectomy
- In pregnancy; medical management but if failed, subtotal thyroidectomy

Thyroid Storm is a rare but life-threatening complication of thyrotoxicosis. It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature. **Iatrogenic thyroxine excess does not usually result in thyroid storm**

Clinical features include:

- Fever > 38.5°c
- Tachycardia
- Confusion and agitation
- Nausea and vomiting
- Hypertension
- Heart failure
- Abnormal liver function test

Management

- Symptomatic treatment e.g. Paracetamol
- Treatment of underlying precipitating event
- Anti-thyroid drugs: e.g. Methimazole or propylthiouracil
- Lugol's iodine
- Dexamethasone - e.g. 4mg IV QDS - blocks the conversion of T4 to T3
- Propranolol

Subacute Thyroiditis (De Quervain's Thyroiditis) is thought to occur following viral infection and typically presents with hyperthyroidism

Features

- Hyperthyroidism
- Painful goiter
- Raised ESR
- Globally ↓ uptake on iodine-131 scan

Tender goitre, hyperthyroidism and raised ESR + globally reduced uptake on technetium thyroid scan is typical (De Quervian)

Management

- Usually self-limiting - most patients do not require treatment
- Thyroid pain may respond to aspirin or other NSAIDs
- In more severe cases steroids are used, particularly if hypothyroidism develops

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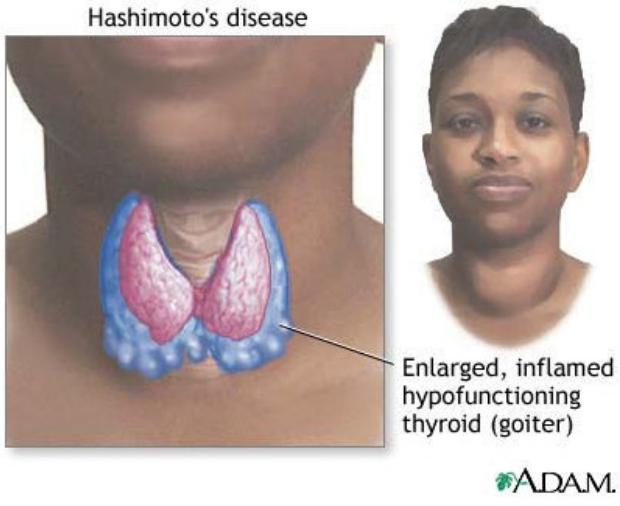
Hashimoto's Thyroiditis is an autoimmune disorder of the thyroid gland. It is typically associated with hypothyroidism although there may be a transient thyrotoxicosis in the acute phase. It is 10 times more common in women

Features

- Features of hypothyroidism
- Goitre: firm, non-tender
- Positive microsomal antibodies, **anti-thyroid peroxidase (Anti-TPO)** and anti-Tg antibodies.



Chronic thyroiditis (Hashimoto's disease) is a slowly developing persistent inflammation of the thyroid which frequently leads to hypothyroidism, a decreased function of the thyroid gland. Middle-aged women are most commonly affected.

Subclinical Hyperthyroidism

is an entity which is gaining increasing recognition. It is defined as:

- Normal $T_3 - T_4$
- ↓ TSH (usually < 0.1 mu/l)

Causes

- Multinodular goitre, particularly in elderly ♀s
- Excessive thyroxine may give a similar biochemical picture

The importance in recognising subclinical hyperthyroidism lies in the potential effect on the cardiovascular system (atrial fibrillation) and bone metabolism (osteoporosis). It may also impact on quality of life and ↑ the likelihood of dementia

Management

- TSH levels often revert back to normal - therefore levels must be persistently low to warrant intervention
- A reasonable treatment option is a therapeutic trial of low-dose antithyroid agents for approximately 6 months in an effort to induce a remission

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Subclinical Hypothyroidism

Basics

- Normal $T_3 - T_4$
- ↑ TSH
- No obvious symptoms

Significance

- Risk of progressing to overt hypothyroidism is 2-5% per year (higher in men)
- Risk ↑ by presence of thyroid autoantibodies

Treat if

- TSH > 10
- Thyroid autoantibodies positive
- Other autoimmune disorder
- Previous treatment of graves' disease

Hypothyroidism

In European countries primary atrophic hypothyroidism is the most cause causes of hypothyroidism, whereas in North America Hashimoto's thyroiditis appears to account for the majority of cases. The reason for this discrepancy is unclear

Causes:

Hypothyroidism affects around 1-2% of women in the UK and is around 5-10 times more common in ♀s than ♂s.

Primary hypothyroidism

1. Primary atrophic hypothyroidism
    - Most common cause in Europe
    - **Autoimmune disease, associated with IDDM, Addison's or pernicious anemia**
    - 5 times more common in women

2. Hashimoto's thyroiditis
    - Autoimmune disease as above **with goitre** (**Anti-TPO**)
    - May cause transient thyrotoxicosis in the acute phase
    - 10 times more common in women

3. After thyroidectomy or radioiodine treatment
4. Drug therapy (e.g. lithium, amiodarone or anti-thyroid drugs such as carbimazole)
5. Dietary iodine deficiency

Secondary hypothyroidism (rare)

1. From pituitary failure
2. Other associated conditions
    - Down's syndrome
    - Turner's syndrome
    - Coeliac disease

A TSH value between 0.5 to 2.5 mU/l is now considered preferable

Management:

Key points

- Initial starting dose of levothyroxine should be lower in elderly patients and those with ischemic heart disease (e.g. 25–50 mcg/day).
- Following a change in thyroxine dose thyroid function tests should be checked after 6-8 weeks
- The therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level. As the majority unaffected people have a TSH value 0.5–2.5 mu/l it is now thought preferable to aim for a TSH in this range. Dosage changes should of course also take account of symptoms
- There is no evidence to support combination therapy with levothyroxine and liothyronine

Side-effects of thyroxine therapy

- Hyperthyroidism: due to over treatment
- ↓ bone mineral density
- Worsening of angina
- Atrial fibrillation

Thyroid function test is usually straight forward:

Abnormality	TSH	F. T4	Interpertation
Thyrotoxicosis (e.g. Graves)	↓	↑	In T3 thyrotoxicosis, T4 will be normal
Primary (atrophic) hypothyroidism	↑	↓	
Secondary hypothyroidism	↓	↓	Steroid therapy is required prior to thyroxine
Sick euthyroid syndrome*	↓**	↓	Common in hospital inpatients
Poor compliance with thyroxine	↑	↔ / ↑	
Steroid therapy	↓	↔	

*now referred to as non-thyroidal illness - **TSH may be normal in some cases

Pendred's Syndrome Autosomal recessive disorder of defective iodine uptake

Features:

- Sensorineural deafness
- Goitre
- Euthyroid or mild hypothyroidism

For the purposes of postgraduate exams pretibial myxedema is associated with thyrotoxicosis. There are however case reports of it been found in hypothyroid patients, especially the diffuse non-pitting variety

Skin Manifestations of Thyroid Diseases:

Hyperthyroidism	Hypothyoridism
• Pretibial myxedema: erythematous, edematous lesions above the lateral malleoli • Thyroid acropachy: clubbing • Scalp hair thinning • ↑ sweating	• Dry (anhydrosis), cold, yellowish skin • Non-pitting edema (e.g. Hands, face) • Dry, coarse scalp hair, loss of lateral aspect of eyebrows • Eczema • Xanthomata

Pruritus can occur in both hyper- and hypothyroidism

Propylthiouracil is traditionally taught as the antithyroid drug of choice in pregnancy. This approach was supported by the 2007 Endocrine Society consensus guidelines. It also has the advantage of being excreted to a lesser extent than carbimazole in breast milk.

Despite this some endocrinologists use carbimazole and the BNF states both drugs may be used in pregnancy. Carbimazole has rarely been associated with aplasia cutis of the neonate

Pregnancy: Thyroid Problems

in pregnancy there is ↑ in the levels of thyroxine-binding globulin (TBG). This causes ↑ in the levels of total thyroxine but does not affect the free thyroxine level

Thyrotoxicosis

- Untreated thyrotoxicosis ↑ the risk of fetal loss, maternal heart failure and premature labour
- **Graves' disease is the most common cause of thyrotoxicosis in pregnancy**. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in second and third trimester

Management

- Propylthiouracil has traditionally been the antithyroid drug of choice. This approach was supported by the 2007 endocrine society consensus guidelines
- Maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- Thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine risk of neonatal thyroid problems
- **Block-and-replace regimes should not be used in pregnancy**
- Radioiodine therapy is contraindicated

Hypothyroidism

Key points

- **Thyroxine is safe during pregnancy**
- Serum thyroid stimulating hormone measured in each trimester and 6-8 weeks post-partum
- Some women require an ↑ dose of thyroxine during pregnancy
- **Breast feeding is safe whilst on thyroxine**

Sick Euthyroid Syndrome: (now referred to as non-thyroidal illness) it is often said that **everything (TSH, thyroxine and T3) is low**. In some cases the TSH level may be normal. Changes are reversible upon recovery from the **systemic illness. Usually in hospitalized patients.**

Thyroid Cancer:

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

Type	%	
Papillary	70%	Often young ♀s - excellent prognosis (associated with FAP)
Follicular	20%	Spreads through blood vessels
Medullary	5%	Cancer of parafollicular cells, secrete calcitonin, part of **ME**N-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's and other **autoimmune** disorders

Management of papillary and follicular cancer

- Total thyroidectomy
- Followed by radioiodine (I-131) to kill residual cells
- Yearly thyroglobulin levels to detect early recurrent disease (only after total thyroid ablation)

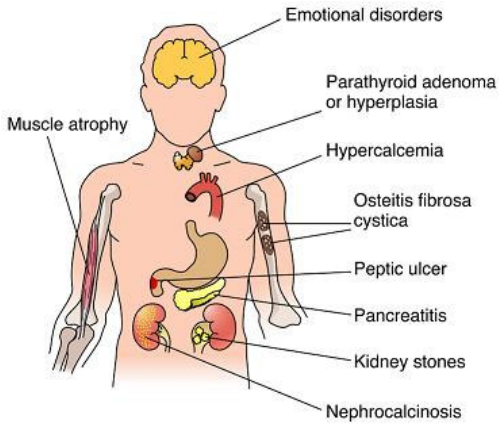
Primary Hyperparathyroidism

In postgraduate exams primary hyperparathyroidism is stereotypically seen in elderly ♀s with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level. It is most commonly due to a solitary adenoma

The PTH level in primary hyperparathyroidism may be normal

Causes of primary hyperparathyroidism

- 80%: solitary adenoma
- 15%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma



Features:

'Bones, stones, abdominal groans and psychic moans'

- Polydipsia, polyuria
- Peptic ulceration/constipation/pancreatitis
- Bone pain/fracture
- Renal stones
- Depression
- Hypertension

Associations

- Hypertension
- Multiple endocrine neoplasia: MEN I and II

Investigations

- Raised calcium, low phosphate
- PTH may be raised or normal
- Technetium-MIBI subtraction scan

Treatment

- IV Fluids
- Total parathyroidectomy
- Bisphosphonates

Hypoparathyroidism

Primary hypoparathyroidism

- ↓ PTH secretion
- E.g. Secondary to thyroid surgery
- Low calcium, high phosphate
- Treat with alfacalcidol

Pseudohypoparathyroidism

- Target cells being insensitive to PTH
- In type I pseudohypoparathyroidism there is a complete receptor defect whereas in type II the cell receptor is intact.
- **Due to abnormality in a G protein**
- Autosomal dominant fashion*
- Associated with low IQ, short stature, shortened 4th and 5th metacarpals
- **Low calcium, high phosphate, high PTH**
- Diagnosis is made by measuring urinary cAMP and phosphate levels following an infusion of PTH. In hypoparathyroidism this will cause ↑ in both cAMP and phosphate levels. In pseudohypoparathyroidism type I neither cAMP nor phosphate levels are ↑ whilst in pseudohypoparathyroidism type II only cAMP rises.

Pseudopseudohypoparathyroidism

- Similar phenotype to pseudohypoparathyroidism but normal biochemistry

*it was previously thought to be an X-linked dominant condition

Diabetes Insipidus

Causes of Cranial DI

- Idiopathic
- Post head injury
- Pituitary surgery
- Craniopharyngiomas
- Histiocytosis X

DIDMOAD is the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)

Causes of nephrogenic DI

- Genetic (primary)
- Electrolytes: hypercalcemia, Hypokalemia
- Drugs: demeclocycline, lithium
- Tubulo-interstitial disease: obstruction, sickle-cell, pyelonephritis

Investigation

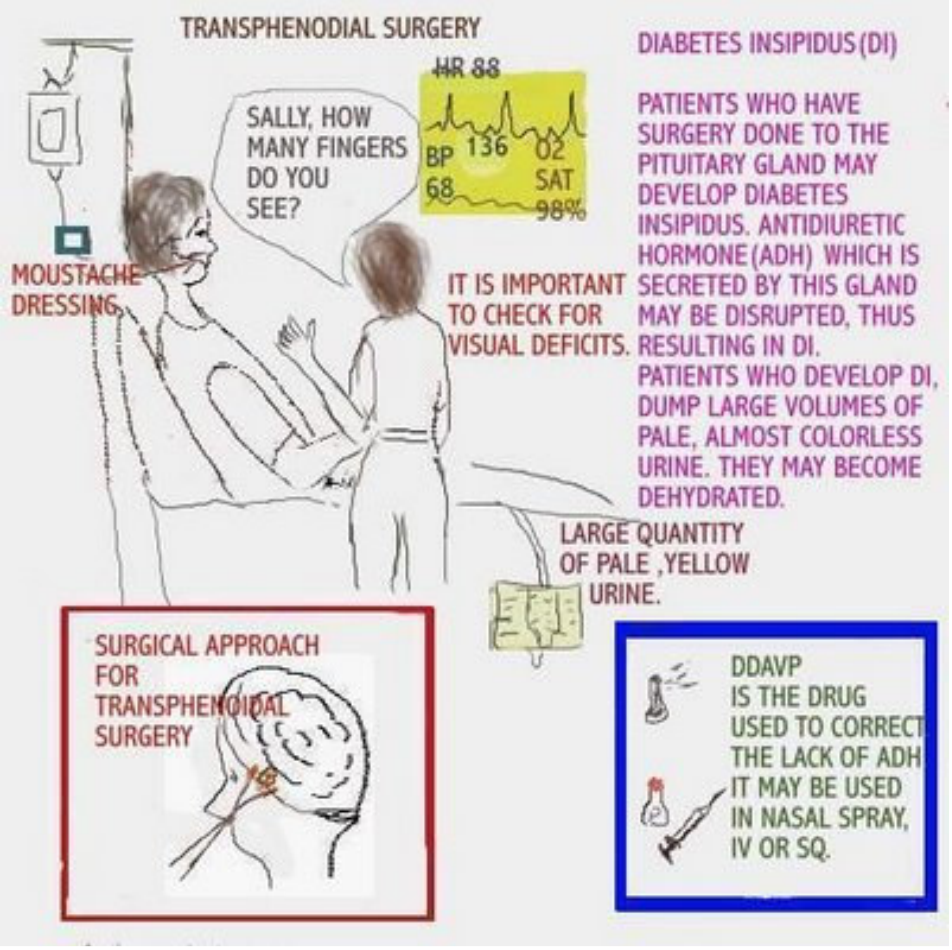
- High plasma osmolarity, low urine osmolarity
- Water deprivation test

Water Deprivation Test

Method

- Prevent patient drinking water
- Ask patient to empty bladder
- Hourly urine and plasma osmolalities

	Starting plasma osm.	Final urine osm.	Urine osm. post-DDAVP
Normal	Normal (275-299)	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300
SIADH	Low	High	---



Diabetes Mellitus

If the patient is symptomatic:

- Fasting glucose ≥7.0 mmol/l
- Random glucose ≥11.1 mmol/l (or after 75g oral glucose tolerance test)

If the patient is asymptomatic the above criteria apply but must be demonstrated on two separate occasions.

Impaired fasting glucose (IFG): fasting glucose 6.1 - 7.0 mmol/l implies impaired fasting glucose
Impaired glucose tolerance (IGT): fasting plasma glucose < 7.0 and OGTT 2-hour 7.8 - 11.1

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by **increasing pancreatic insulin secretion** and hence are only effective if functional B-cells are present.

Common adverse effects

- Hypoglycaemic episodes (more common with long acting preparations such as chlorpropamide)
- ↑ appetite and weight gain

Rarer adverse effects

- Syndrome of inappropriate ADH secretion
- Bone marrow suppression
- Liver damage (cholestatic)
- Photosensitivity
- Peripheral neuropathy
- **Sulfonylureas should be avoided in breast feeding and pregnancy**

Metformin is a **biguanide** used mainly in the treatment of type 2 diabetes mellitus. It has a number of actions which improves glucose tolerance (see below). Unlike sulphonylureas it does not cause hypoglycemia and weight gain and is therefore first-line if the patient is overweight. Metformin is also used in polycystic ovarian syndrome and non-alcoholic fatty liver disease

Mechanism of action

- ↑ Insulin sensitivity
- ↓ hepatic gluconeogenesis
- May also ↓ gastrointestinal absorption of carbohydrates

Metformin should be titrated slowly, leave at least 1 week before increasing dose

Gastrointestinal side-effects are more likely to occur if metformin is not slowly titrated up. The BNF advises leaving at least 1 week before increasing the dose. If a patient is intolerant to standard metformin then modified release preparations should be tried

Adverse effects

- Gastrointestinal upsets are common (nausea, anorexia, diarrhea), intolerable in 20%
- ↓ vitamin B12 absorption - rarely a clinical problem
- Lactic acidosis* with severe liver disease or renal failure
- High dose (>2gm) interferes with enterohepatic circulation of bile salt → diarrhea.

Contraindications**

- Chronic kidney disease: NICE recommend reviewing metformin if the creatinine is > 130 µmol/l and stopping metformin if > 150 µmol/l
- Do not use during suspected episodes of tissue hypoxia (e.g. Recent MI, sepsis)
- Alcohol abuse is a relative contraindication
- Stop 2 days before general anaesthetic, restart when renal function normal
- Stop prior to IV contrast e.g. Angiography, restart when renal function normal

*it is now increasingly recognised that lactic acidosis secondary to metformin is rare, although it remains important in the context of postgraduate exams
**metformin is now sometimes used in pregnancy, for example in women with polycystic ovary

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Glitazones are agonists of PPAR-gamma receptors

Thiazolidinediones are a new class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and ↓ peripheral insulin resistance

Peroxisome Proliferator-Activated Receptor Gamma (PPAR-gamma receptor) is an intracellular nuclear receptor. Its natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function

Adverse effects

- **Weight gain**
- Liver impairment: monitor LFTs
- **Fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is ↑ if the patient also takes insulin**
- Recent studies have indicated an ↑ risk of fractures
- Rosiglitazone is not recommended for use in patients with ischemic heart disease or peripheral arterial disease. The risk of complications may be ↑ if rosiglitazone is combined with insulin

NICE guidance on thiazolidinediones

- Only continue if there is a reduction of > 0.5 percentage points in HbA_1c in 6 months

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Exenatide causes vomiting

GLP-1 and the New Drugs: a number of new drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a **hormone released by the small intestine in response to an oral glucose load**

Whilst it is well known that with insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 DM. In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the **incretin effect**. This effect is largely mediated by GLP-1 and is known to be ↓ in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue or inhibiting its breakdown, is therefore the target of two recent classes of drug

Glucagon-Like Peptide-1 (GLP-1) Mimetics (e.g. exenatide)

- ↑ insulin secretion and inhibit glucagon secretion
- Licensed for use in T2DM
- Must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal
- May be combined with metformin, a sulfonylurea or a thiazolidinedione
- Typically results in weight loss
- Major adverse effect is nausea and vomiting
- The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide:
    - increased risk of severe pancreatitis
    - increased risk of renal impairment

NICE guidelines on the use of Exenatide

- Should be used only when insulin would otherwise be started, obesity is a problem (BMI > 35 kg/m^2) and the need for high dose insulin is likely
- Continue only if beneficial response occurs and is maintained (> 1.0 percentage point HbA_1c reduction and weight loss > 3% in 6 months)

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors (e.g. Vildagliptin, sitagliptin)

- Oral preparation
- Trials show that the drugs are relatively well tolerated with no ↑ incidence of hypoglycemia
- Do not cause weight gain

NICE Guidelines on DPP-4 Inhibitors

- Continue DPP-4 inhibitor only if there is ↓ of > 0.5 percentage points in HbA_1c in 6 months
- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

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NICE Updates On The Management Of T2DM in 2009. Key points are:

Exenatide should only be used in combination with Metformin, a Sulfonylurea or both.

Dietary advice

- Encourage high fibre, low glycaemic index sources of carbohydrates
- Include low-fat dairy products and oily fish
- Control the intake of foods containing saturated fats and trans fatty acids
- Limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- **Discourage use of foods marketed specifically at people with diabetes**
- Initial target weight loss in an overweight person is 5-10%

HbA_1c

- The general target for patients is 6.5%. HbA_1c levels below 6.5% should not be pursued
- However, individual targets should be agreed with patients to encourage motivation
- HbA_1c should be checked every 2-6 months until stable, then 6 monthly

Blood pressure

- Target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
- ACE inhibitors are first-line

The NICE treatment algorithm has become much more complicated following the introduction of new therapies for T2DM. Below is a vey selected group of points from the algorithm:

- NICE still suggest a trial of lifestyle interventions first (many local protocols now recommend **starting metformin upon diagnosis**)
- Usually metformin is first-line, followed by a sulfonylurea if the HbA_1c remains > 6.5%
- If the patient is at risk from hypoglycemia (or the consequences of) then a DPP-4 inhibitor or thiazolidinedione should be considered rather than a sulfonylurea
- Meglitinides (insulin secretagogues) should be considered for patients with an erratic lifestyle
- If HbA_1c > 7.5% then consider human insulin
- Metformin treatment should be continued after starting insulin
- Exenatide should be used only when insulin would otherwise be started, obesity is a problem (BMI > 35 kg/m^2) and the need for high dose insulin is likely. Continue only if beneficial response occurs and is maintained (> 1.0 percentage point HbA_1c reduction in 6 months and weight loss > 5% at 1 year)

Meglitinides - stimulate insulin release – suitable for erratic lifestyle and erratic eating schedule

Particularly useful for post-prandial hyperglycemia as patients take them shortly before meals

Starting insulin

- Usually commenced if HbA_1c > 7.5%
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need

Other risk factor modification

- Aspirin to all patients > 50 years and to younger patients with other significant risk factors
- The management of blood lipids in T2DM has changed slightly. Previously all patients with T2DM > 40-years-old were prescribed statins. Now patients > 40-years-old who have no obvious cardiovascular risk (e.g. Non-smoker, not obese, normotensive etc) and have a cardiovascular risk < 20%/10 years do not need to be given a statin.
- If serum cholesterol target is not reached consider increasing simvastatin to 80mg HS.
- If target still not reached consider using a more effective statin (e.g. Atorvastatin) or adding ezetimibe
- Target total cholesterol is < 4.0 mmol/l
- If serum triglyceride levels are > 4.5 mmol/l prescribe fenofibrate

Diabetic Neuropathy: NICE guidance on the management of DM neuropathy of 2010:

- First-line: oral duloxetine. Oral amitriptyline if duloxetine is contraindicated.
- Second-line treatment: if first-line treatment was with duloxetine, switch to amitriptyline or pregabalin, or combine with pregabalin. If first-line treatment was with amitriptyline, switch to or combine with pregabalin
- Other options: pain management clinic, tramadol (not other strong opioids), topical lidocaine for localised pain if patients unable to take oral medication
- Consider capsaicin ointment (red pepper extract) local application

Gastroparesis

- Symptoms include erratic blood glucose control, bloating and vomiting
- Management options include metoclopramide, domperidone or erythromycin

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↑ Insulin with ↓ C-Peptide level points to a diagnosis of insulin abuse
C-Peptide level ↑ with Sulfonylurea abuse

Hypoglycemia:

Causes

- Insulinoma - ↑ ratio of proinsulin to insulin
- Self-administration of insulin/sulphonylureas
- Liver failure
- Addison's disease
- Alcohol

Other possible causes in children

- Nesidioblastosis - β cell hyperplasia

Average Plasma Glucose = (2 * HbA_1c) - 5

Glycosylated hemoglobin (HbA_1c) is the most widely used measure of long-term glycaemic control in DM. HbA_1c is produced by the glycosylation of hemoglobin at a rate proportional to the glucose concentration. The level of HbA_1c therefore is dependent on

- Red blood cell lifespan
- Average blood glucose concentration

HbA_1c is generally thought to reflect the blood glucose over the previous '2-3 months' although there is some evidence it is weighed more strongly to glucose levels of the past 2-4 weeks

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Hyperosmolar Hyperglycaemic State:

The American Diabetes Association criteria for the diagnosis of hyperosmolar hyperglycaemic state (HHS) are as follows:

1. Glucose > 33.3 mmol/l
2. pH > 7.30
3. Serum bicarbonate > 15 mmol/l
4. Serum osmolality > 320 mosmol/kg
5. Traces of ketones may be present in urines

Diabetic Ketoacidosis

The most common precipitating factors of DKA are infection, missed insulin doses and MI.

The low-insulin condition in DKA stimulate → lipolysis → production of ketone bodies, β-hydroxybutyrate and acetoacetate, which can be used as metabolic fuel

American Diabetes Association diagnostic criteria are as follows:

- Blood glucose >13.8 mmol/l
- pH < 7.30
- Serum bicarbonate <18 mmol/l
- Anion gap > 10
- Ketonemia

Management

- Fluid replacement: most patients are depleted ≈ 5-8 litres. 0.9% saline is used initially
- **Insulin**: an intravenous **infusion** should be started at **6U/hour**. Once blood glucose is < 15 mmol/l an infusion of 5% dextrose should be started
- Correction of Hypokalemia
- LMWH to prevent DVT

Complications of DKA and its treatment

- Gastric stasis
- Cerebral edema
- Thromboembolism
- Acute respiratory distress syndrome
- Acute renal failure

Pregnancy: Diabetes Mellitus

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It **complicates around 1 in 40 pregnancies**

Risk factors for gestational diabetes

- BMI of > 30 kg/m^2
- Previous macrosomic baby weighing 4.5 kg or above.
- Previous gestational diabetes
- First-degree relative with diabetes
- Family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- If a women has had gestational diabetes previously an oral glucose tolerance test (OGTT) should be performed at 16-18 weeks and at 28 weeks if the first test is normal
- Women with any of the other risk factors should be offered an OGTT at 24–28 weeks

NICE issued guidelines on the management of diabetes mellitus in pregnancy in 2008

Management

- Weight loss for women with BMI of > 27 kg/m^2
- Stop oral hypoglycaemic agents, apart from metformin*, and commence insulin
- Folic acid 5 mg/day from pre-conception to 12 weeks gestation
- Detailed anomaly scan at 18-20 weeks including 4-chamber view of the heart and outflow tracts
- Tight glycaemic control ↓ complication rates
- Treat retinopathy as can worsen during pregnancy

Women who develop gestational diabetes should stop taking hypoglycaemic medication following delivery. A fasting glucose should be checked at the 6 week postnatal check

*there is increasing evidence that metformin is safe during pregnancy

Type 1 Diabetes Mellitus is caused by autoimmune destruction of the β-cells of the pancreas. **Identical twins show a genetic concordance of 40%.** It is associated with HLA-DR3 and DR4. It is inherited in a polygenic fashion

Type 2 diabetes mellitus is thought to be caused by a relative deficiency of insulin and the phenomenon of insulin resistance. Age, obesity and ethnicity are important aetiological factors. There is almost **100% concordance in identical twins** and no HLA associations.

Adhesive capsulitis (frozen shoulder) is strongly associated with diabetes type-I with as many as 40% of patients developing this problem at some stage

Hemochromatosis is an example of secondary diabetes → damages pancreas.

Type 1 DM Pathophysiology:

- Autoimmune disease
- Antibodies against β cells of pancreas
- HLA DR4 > HLA DR3
- Various antibodies such as islet-associated antigen (IAA) antibody and glutamic acid decarboxylase (GAD) antibody are detected in patients who later go on to develop type 1 DM - their prognostic significance is not yet clear

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Maturity-Onset Diabetes Of The Young (MODY) is characterized by the development of type 2 diabetes mellitus in patients < 25 years old. It is typically inherited as an autosomal dominant condition. Over six different genetic mutations have so far been identified as leading to MODY. **Ketosis is not a feature at presentation.** Usually there is a strong family history

MODY= Auto Dominant

MODY 3

- 60% of cases
- Due to a defect in the HNF-1 α gene (Hepatocyte Nuclear Factor).

MODY 2

- 20% of cases
- Due to a defect in the glucokinase gene

MODY 1

- < 10%
- Due to defect in HNF-4 α gene.

Patients on insulin cannot hold a HGV licence

DVLA

The April 2009 AKT feedback report made specific mention of fitness to drive rules.

The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles (HGVs) tend to be much stricter

Specific rules

- If on insulin then cannot hold HGV licence*

- If on insulin then patient can drive a car as long as they have hypoglycaemic awareness and no relevant visual impairment
- If on tablets, exenatide or gliptin no need to notify DVLA
- If diet controlled alone and no relevant complications (e.g. Maculopathy) then no requirement to inform DVLA

*there are complex exceptions to this rule, but these are not relevant for the purposes of the exam

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Insulinoma is diagnosed with supervised prolonged fasting

CT of the pancreas is also useful in demonstrating a lesion

Insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells

Basics

- Most common pancreatic endocrine tumour
- 10% malignant, 10% multiple
- Of patients with multiple tumours, 50% have MEN-1

Features

- Of hypoglycemia: typically early in morning or just before meal, e.g. Diplopia, weakness etc
- Rapid weight gain may be seen
- High insulin, raised proinsulin:insulin ratio
- High C-peptide

Diagnosis

- Supervised, prolonged fasting (up to 72 hours)
- CT pancreas

Insulin stress tests are also occasionally used to differentiate Cushing's from pseudo-Cushing

Insulin Stress Test

Basics

- Used in investigation of hypopituitarism
- IV insulin given, GH and cortisol levels measured
- With normal pituitary function GH and cortisol should rise

Contraindications

- Epilepsy
- Ischemic heart disease
- Adrenal insufficiency

Cushing's Syndrome:

Cushing's disease (pituitary tumor) is the most common, non-iatrogenic, cause of Cushing's syndrome

Causes

ACTH dependent causes

- Cushing's disease (80%): pituitary tumour secreting ACTH producing adrenal hyperplasia
- Ectopic ACTH production (5-10%): e.g. Small cell lung cancer

Small cell lung cancer accounts 50-75% of case of ectopic ACTH

Adrenal carcinoma and cardiac myxoma are causes of ACTH independent Cushing's syndrome

ACTH independent causes

- Iatrogenic: steroids
- Adrenal adenoma (5-10%)
- Adrenal carcinoma (rare)
- Carney complex: syndrome including cardiac myxoma
- Micronodular adrenal dysplasia (very rare)

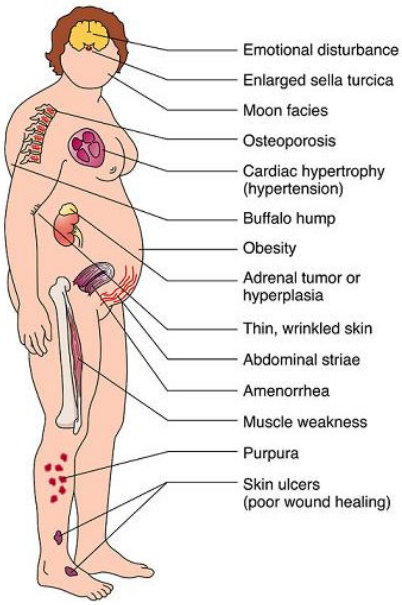
Pseudo-Cushing's

- Mimics Cushing's
- Often due to alcohol excess or severe depression
- Causes false positive dexamethasone suppression test or 24 hr urinary free cortisol
- Insulin stress test may be used to differentiate

The overnight dexamethasone suppression test is the best test to diagnosis Cushing's syndrome

There is some debate as to whether a 24 hour urinary free cortisol or an overnight dexamethasone suppression test should be used to screen patients for Cushing's. The overnight dexamethasone suppression test has however been shown to be more sensitive and is now much more commonly used in clinical practice. If this is not offered then 24 hour urinary free cortisol is the next best answer

The high-dose dexamethasone suppression test is used to help differentiate the cause of Cushing's syndrome.



Investigations are divided into confirming Cushing's syndrome and then localising the lesion. A **hypokalaemic metabolic alkalosis** may be seen, along with impaired glucose tolerance. Ectopic ACTH secretion (e.g. secondary to small cell lung cancer) is characteristically associated with very low potassium levels. An insulin stress test is used to differentiate between true Cushing's and pseudo-Cushing.

Tests to confirm Cushing's syndrome:

- Overnight dexamethasone suppression test (most sensitive)
- 24 hr urinary free Cortisol

Localisation tests: the first-line localisation is 9am and midnight plasma ACTH (and cortisol) levels. If ACTH is suppressed then ACTH independent cause is likely such as an adrenal adenoma

High-dose dexamethasone suppression test

- If pituitary source then cortisol suppressed
- If ectopic/adrenal then no change in cortisol

CRH (corticotrophin-releasing hormone) stimulation

- If pituitary source then cortisol rises
- If ectopic/adrenal then no change in cortisol

Petrosal sinus ACTH sampling may be needed to differentiate between pituitary and ectopic ACTH

Liddle's syndrome: Hypokalemia + Hypertension

Liddle's Syndrome is an autosomal dominant disorder that mimics hyperaldosteronism, resulting in Hypokalemia associated with hypertension. It is thought to be caused by disordered sodium channels in the distal tubules leading to increased reabsorption of sodium, leading to hypokalemia and **alkalosis**.

↓ rennin - ↓ aldesterone

Treatment is with either amiloride or triamterene

Gitelman's syndrome: normotension with Hypokalemia

Gitelman's Syndrome: defect in the thiazide-sensitive Na^+ Cl^- transporter in the distal convoluted tubule

Little minded people (Liddle) would've HTN but gentlemen would not develop HTN

Features

- Hypokalemia
- **Hypomagnesemia**
- Hypocalciuria
- **Metabolic alkalosis**
- Normotension

↑ rennin - ↑ aldesterone

Bartter's syndrome is associated with normotension

Bartter's Syndrome is an inherited cause (usually autosomal recessive) of severe Hypokalemia due to defective chloride absorption at the Na^+ K^+ $2Cl^-$ cotransporter in the ascending loop of Henle. It should be noted that is associated with normotension (unlike other endocrine causes of Hypokalemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension)

Features:

- Usually presents in childhood, e.g. Failure to thrive
- Polyuria, polydipsia
- Renal stones, nephrocalcinosis is commom
- Weakness

- Hypokalemia
- **NO Hypomagnesemia**
- Normotension

↑ rennin - ↑ aldesterone

Bilateral idiopathic adrenal hyperplasia is the most common cause of primary hyperaldosteronism

Primary Hyperaldosteronism: primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed **Conn's Syndrome**. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the cause in 70% of cases. Differentiating between the two is important as this determines treatment. Adrenal carcinoma is an extremely rare cause of primary hyperaldosteronism. Aldesterone (↑ Na^+ absorption – excrete K^+ and H^+)

Features

- Hypertension
- Hypokalemia (e.g. Muscle weakness)
- Alkalosis
- Hypernatremia
- Not related to posture

Investigations: the best is Renin:Aldosterone Ratio

- High serum aldosterone
- Low serum renin
- High-resolution CT abdomen

Renal Artery Stenosis:	Conn's Syndrome
• ↑ Renin • ↑ Aldosterone • ↑ BP • ↑ On standing	• ↓ Renin • ↑ Aldosterone • ↑ BP • Not affected by posture

Management

- Na^+ restriction
- Adrenal adenoma: surgery
- Bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. Spironolactone

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Typical history of Addison's: abdominal pain and vomiting. Patients may have a history of other autoimmune conditions such as thyroid disorders. Steroids should be given as soon as possible

Addison's Disease: autoimmune destruction of the adrenal glands is the commonest cause of hypoadrenalism in the UK, accounting for 80% of cases

Features

- Lethargy, weakness, anorexia, nausea & vomiting, weight loss
- Hyperpigmentation, vitiligo, loss of pubic hair in women
- Crisis: collapse, shock, pyrexia

Other causes of hypoadrenalism

1. Primary causes
   - Tuberculosis
   - Metastases (e.g. Bronchial Carcinoma)
   - Meningococcal septicemia (Waterhouse-Friderichsen Syndrome)
   - HIV
   - Antiphospholipid Syndrome
   - Severe illness
2. Secondary causes
   - Pituitary disorders (e.g. Tumours, Irradiation, Infiltration)
   - Drugs: ACE-I – Heparin – Lead poisoning
3. Exogenous glucocorticoid therapy
4. Pseudohypoaldosteronism: due to primary aldosterone resistance (rare, but may occur due to Spirnolactone)

Dehydroepiandrosterone is the most abundant circulating adrenal steroid. Adrenal glands are the main source of DHEA in ♀s - loss of functioning adrenal tissue as in Addison's disease may result in symptoms secondary to androgen deficiency, such as loss of libido. Research is ongoing as to whether routine replacement of DHEA is beneficial

The short synacthen test is the best test to diagnose Addison's disease

Hyponatremia and high potassium in a patient with lethargy is highly suggestive of Addison's

Investigations: in a patient with suspected Addison's disease the definite investigation is a short ACTH test. Plasma cortisol is measured before and 30 minutes after giving Synacthen 250ug IM. Adrenal autoantibodies such as anti-21-hydroxylase may also be demonstrated

Associated electrolyte abnormalities

- Hyperkalemia
- Hyper-Renin
- Hypo-Aldosterone
- Hyponatremia
- Hypoglycemia
- Metabolic acidosis (Hypo pH)

SIADH

Criteria:

- Normal Renal, Normal Adrenal and Normal Thyorid
- Hyponatremia <135 mEq/L
- Hypotonic plasma - P_{Osm} <270 mOsm/kg.
- Inappropriately ↑ urine osmolality
- Urine sodium >20 mEq/L (inappropriate natriuresis)

Causes:

1. Malignancy
   - Especially small cell lung cancer
   - Also: pancreas, prostate

2. Neurological
   - Stroke
   - Subarachnoid hemorrhage
   - Subdural hemorrhage
   - Meningitis/encephalitis/abscess

3. Infections
   - TB
   - Pneumonia

4. Drugs
   - Sulfonylureas
   - SSRIs, tricyclics

Other points to diagnose:

- Maintained hypervolemia
- Suppression of renin-angiotensin system (RAS)
- No equal concentration of atrial natriuretic peptide
- ↓ BUN
- Normal S.Creatinine
- ↓ uric acid
- ↓ albumin
- Normal Acid-Base, K^+ balance

- Carbamazepine
- Vincristine
- Cyclophosphamide

5. Other causes
   - Positive end-expiratory pressure (PEEP)
   - Porphyrias

Treatment:
- Demeclocycline

Pheochromocytoma: is a rare catecholamine secreting neuroendocrine tumor of the medulla of the adrenal glands (originating in the chromaffin cells), or extra-adrenal chromaffin tissue. It secretes excessive amounts of catecholamines, usually adrenaline if in the adrenal gland (not extra-adrenal) and noradrenaline. Extra-adrenal paragangliomas (extra-adrenal pheochromocytomas) are closely related, though less common. About 10% are familial and may be associated with MEN type II, neurofibromatosis and Von Hippel-Lindau syndrome.

Adrenal gland is the only source of adrenaline in the body

Signs and Symptoms:	
• ↑ Heart Rate, Palpitations • ↑BP, including paroxysmal (sporadic, episodic) ↑ blood pressure, which sometimes can be more difficult to detect. • Orthostatic hypotension (a fall in systolic blood pressure greater than 20 mmHg or a fall in diastolic blood pressure greater than 10 mmHg on making the patient stand)	• Skin (Hot Flushes, ?Pigmentation) • Flank Pain • Anxiety often resembling that of a panic attack • Diaphoresis • Headaches, Pallor, Weight loss • Localized amyloid deposits found microscopically • Elevated blood glucose level.
Basics:	
• Familial 10% • Bilateral in 10% • Malignant in 10%	• Extra-adrenal in 10% (most common site = organ of zuckerkandl, adjacent to the bifurcation of the aorta)

Pheochromocytoma: do 24 hr urinary catecholamines, not VMA

24hr urinary collection of catecholamines is preferred to one of vanillylmandelic acid as it has a higher sensitivity. Three 24 hour collections are needed as some patients have intermittently raised levels

Surgery is the definitive management. The patient must be pre-stabilized with medical management:

PHEochromocytoma - give **PHE**noxybenzamine before beta-blockers

- α-blocker (e.g. **Phenoxybenzamine**), given before a
- β-blocker (e.g. Propranolol)

Hypokalemia and Hypertension

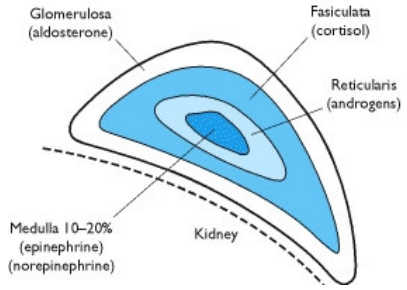
For postgraduate exams it is useful to be able to classify the causes of Hypokalemia in to those associated with hypertension, and those which are not

Hypokalemia with hypertension:	Hypokalemia without hypertension:
• Cushing's syndrome • Conn's syndrome (primary hyperaldosteronismm) • Liddle's syndrome • 11-β-hydroxylase deficiency* • Carbenoxolone (anti-ulcer drug) • High liquorice intake	• Diuretics • GI loss (e.g. diarrhea, vomiting) • Renal tubular acidosis (type 1 and 2**) • Bartter's syndrome • Gitelman syndrome

*21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension. It is associated with precocious puberty in boys.
**type 4 renal tubular acidosis is associated with Hyperkalemia

GFR = ACD

- Zona **G**lomerulosa (on outside): mineralocorticoids, mainly **A**ldosterone
- Zona **F**asciculata (middle): glucocorticoids, mainly **C**ortisol
- Zona **R**eticularis (on inside): androgens, mainly **D**ehydroepiandrosterone



Dynamic Pituitary Function Test is used to assess patients with suspected primary pituitary dysfunction

Insulin, TRH and LHRH are given to the patient following that the serum glucose, cortisol, growth hormone, TSH, LH and FSH levels are recorded at regular intervals. Prolactin levels are also sometimes measured*

A normal dynamic pituitary function test has the following characteristics:

- GH level rises > 20mu/l
- Cortisol level rises > 550 mmol/l
- TSH level rises by > 2 mu/l from baseline level
- LH and FSH should double

*dopamine antagonist tests using metoclopramide may also be used in the investigation of hyperprolactinemia. A normal response is at least a two-fold rise in prolactin. A blunted prolactin response suggests a prolactinoma

Pituitary Tumours:

Hormones secreted

- PRL - 35%
- No obvious hormone, 'non-functioning', 'chromophobe' - 30%
- GH - 20%
- PRL and GH - 7%
- ACTH - 7%
- Others: TSH, LH, FSH - 1%

Growth hormone (GH) is an anabolic hormone secreted by the somatotroph cells of the anterior lobe of the pituitary gland. It has actions on multiple organ systems and is important in postnatal growth and development. Growth hormone is also responsible for changes in protein, lipid, and carbohydrate metabolism

Mechanism of action

- Acts on a transmembrane receptor for growth
- Binding of GH to the receptor leads to receptor dimerization
- Acts directly on tissues and also indirectly via insulin-like growth factor 1 (IGF-1), primarily secreted by the liver

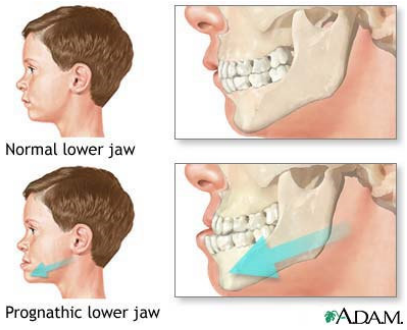
Conditions associated with GH disorders

- Excess GH: acromegaly
- GH deficiency: resulting in short stature

Acromegaly there is excess growth hormone secondary to a pituitary adenoma in over 95% of cases. A minority of cases are caused by ectopic GHRH or GH production by tumours e.g. pancreatic.

Features

- Coarse, oily skin , large tongue, prognathism, interdental spaces
- Spade-like hands, ↑ in shoe size
- Sweating due to **sweat gland hypertrophy**
- Features of pituitary tumour: hypopituitarism, headaches, bitemporal hemianopia
- Raised prolactin in 1/3 of cases → galactorrhoea
- 6% of patients have MEN-1



Complications

- Hypertension
- Diabetes (>10%)
- Cardiomyopathy
- Colorectal cancer

Acromegaly is associated with systemic rather than pulmonary hypertension.

Investigations: Growth hormone (GH) levels vary during the day and are therefore not diagnostic. The definitive test is the oral glucose tolerance (OGTT) with serial GH measurements. Serum IGF-1 may also be used as a screening test and is sometimes used to monitor disease

Disorder	Investigation of choice
Cushing	Overnight Dexamethasone Test
Cushing- vs. Pseudo-cushing	Insulin Stress Test
Addison	Short Synacthen Test
Pheochromocytoma	24^{H} Urinary Catecholamines
Acromegaly	Oral Glucose Tolerance Test

Oral glucose tolerance test

- In normal patients GH is suppressed to < 2 mu/L with hyperglycemia
- In acromegaly there is no suppression of GH
- May also demonstrate impaired glucose tolerance which is associated with acromegaly

A pituitary MRI may demonstrate a pituitary tumour

Management:

Trans-sphenoidal surgery is first-line treatment for acromegaly in the majority of patients

Dopamine agonists

- For example **bromocriptine.**
- The first effective medical treatment for acromegaly, however now superseded by somatostatin analogues
- Effective only in a minority of patients

Somatostatin analogue

- For example **octreotide**
- Effective in 50-70% of patients
- May be used as an adjunct as it helps to control cardiometabolic risk factors prior to surgery.

Pegvisomant

- GH receptor antagonist - prevents dimerization of the GH receptor
- Once daily S/C administration
- Very effective - ↓ IGF-1 levels in 90% of patients to normal
- Doesn't ↓ tumour volume therefore surgery still needed if mass effect

External irradiation is sometimes used for older patients or following failed surgical/medical treatment

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Prolactin is secreted by the anterior pituitary gland with release being controlled by a wide variety of physiological factors. **Dopamine acts as** the primary **prolactin** releasing **inhibitor** and hence dopamine agonists such as bromocriptine may be used to control galactorrhoea. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Prolactin is unique amongst the pituitary hormones in being tonically (continuous) inhibited by the hypothalamus

Features of excess prolactin

- Men: impotence, loss of libido, galactorrhoea
- Women: amenorrhoea, galactorrhoea

Causes of raised prolactin

- Prolactinoma
- Pregnancy
- Estrogens
- Physiological: stress, exercise, sleep
- Acromegaly: 1/3 of patients
- Polycystic ovarian syndrome

- **PRIMARY HYPOTHYROIDISM** (due to thyrotrophin releasing hormone (TRH) stimulating prolactin release)

Drug causes of raised prolactin

- Metoclopramide, domperidone
- Phenothiazines
- Haloperidol
- Very rare: SSRIs, opioids

Prolactinoma management - medical therapy is almost always first-line

Prolactinomas are unusual as **medical therapy is first line**, **even if visual field defects are present**. The main indications for surgery are tumours resistant to dopamine agonists

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Gynaecomastia describes an abnormal amount of breast tissue in ♂s and is usually caused by ↑ estrogen:androgen ratio. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia

- Physiological: normal in puberty
- Syndromes with androgen deficiency: kallman's, klinefelter's
- Testicular failure: e.g. Mumps
- Testicular cancer e.g. Seminoma secreting HCG
- Liver disease
- Ectopic tumour secretion
- **HYPERTHYROIDISM NOT HYPOTHYROIDISM**
- **Hemodialysis**

Drug causes of gynaecomastia

- Spironolactone (most common drug cause)
- Cimetidine
- Digoxin
- Cannabis
- Finasteride
- Estrogens, anabolic steroids

Very rare drug causes of gynaecomastia

- Tricyclics
- Isoniazid
- Calcium channel blockers
- Heroin
- Busulfan
- Methyldopa

Metabolic Syndrome: Unfortunately there are a number of competing definitions of the metabolic syndrome around at the present time. It is thought that the key pathophysiological factor is insulin resistance.

SIGN recommend using criteria similar to those from the American Heart Association. **For a diagnosis of metabolic syndrome at least 3 of the following should be identified**:

- Elevated **waist circumference**: men > 102 cm, women > 88 cm
- Elevated **triglycerides**: > 1.7 mmol/l
- ↓ **HDL**: < 1.03 mmol/l in ♂s and < 1.29 mmol/l in ♀s
- Raised **blood pressure**: > 130/85 mmHg, or active treatment of hypertension
- Raised **fasting plasma glucose** > 5.6 mmol/l, or previously diagnosed type 2 diabetes

The **I**nternational **D**iabetes **F**ederation produced a consensus set of diagnostic criteria in 2005, which are now widely in use. These require the presence of **central obesity** (defined as waist **circumference** > 94cm for Europid men and > 80cm for Europid women, with ethnicity specific values for other groups) plus any two of the following four factors:

- Raised **triglycerides** level: > 1.7 mmol/L, or specific treatment for this lipid abnormality
- ↓ **HDL** cholesterol: < 1.03 mmol/L in ♂s and < 1.29 mmol/L in ♀s, or specific treatment for this lipid abnormality
- Raised **blood pressure**: > 130/85 mm Hg, or active treatment of hypertension
- Raised **fasting plasma glucose** > 5.6 mmol/L, or previously diagnosed type 2 diabetes

In 1999 the **W**orld **H**ealth **O**rganization produced diagnostic criteria which required the presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following:

- **Blood pressure**: > 140/90 mmHg
- Dyslipidemia: **triglycerides**: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (**HDL**-C) < 0.9 mmol/L (♂), < 1.0 mmol/L (♀)
- **Central obesity**: waist:hip ratio > 0.90 (♂), > 0.85 (♀), and/or body mass index > 30 kg/m^2
- **Microalbuminuria**: urinary albumin excretion ratio > 20 mg/min or albumin:creatinine ratio > 30 mg/g

Other associated features include:

- **Raised uric acid levels (Hyperuricemia)**
- **Non-alcoholic fatty liver disease**
- **Polycystic ovarian syndrome**

Obesety:

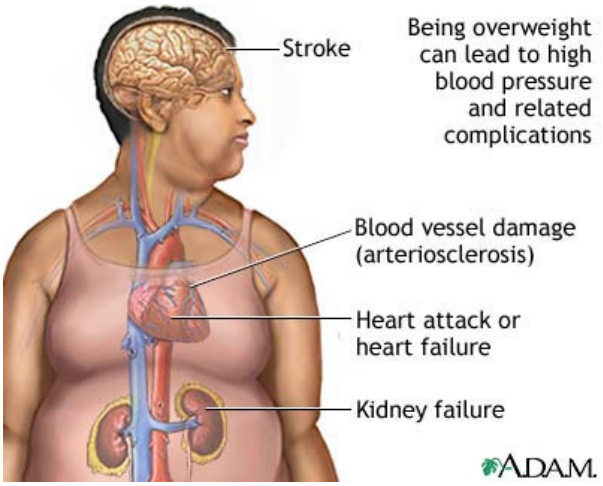
BMI	Normal: 18-25	Overweight: 26-30	Obese-I: 31-35	Obese-II 35-40	Morbid O.> 40

Therapeutic options: The management of obesity consists of a step-wise approach:

- Conservative: diet, exercise
- Medical
- Surgical

Orlistat is a pancreatic lipase inhibitor used in the management of obesity. Adverse effects include faecal urgency/incontinence and flatulence. A lower dose version is now available without prescription ('Alli'). NICE have defined criteria for the use of orlistat. It should only be prescribed as part of an overall plan for managing obesity in adults who have:

- BMI of 28 kg/m^2 or more with associated risk factors, or
- BMI of 30 kg/ m^2 or more
- Continued weight loss e.g. 5% at 3 months
- Orlistat is normally used for < 1 year



Sibutramine

- Withdrawn January 2010 by the European Medicines Agency due to an increased risk of cardiovascular events
- Centrally acting appetite suppressant (inhibits uptake of serotonin and noradrenaline at hypothalamic sites that regulate food intake)
- Adverse effects include hypertension, constipation, headache, dry mouth, insomnia and anorexia
- Contraindicated in psychiatric illness, hypertension, IHD, stroke, arrhythmias

Rimonabant, a specific CB1 cannabinoid receptor antagonist, was withdrawn in October 2008 after the European Medicines Agency warned of serious psychiatric problems including suicide

A guide to deciding the initial level of intervention to discuss

BMI classification	Waist circumference			Co-morbidites present
	Low	High	Very high	
Overweight				
Obesity I				
Obesity II				
Obesity III				

- General advice on healthy weight and lifestyle.
- Diet and physical activity.
- Diet and physical activity; consider drugs.
- Diet and physical activity; consider drugs; consider surgery.

Obesity - NICE bariatric referral cut-offs

- With risk factors (T2DM, BP etc): > 35 kg/m^2
- no risk factors: > 40 kg/m^2

Biliopancreatic diversion with duodenal switch is a primarily malabsorptive procedure and reserved for patients who are very obese.

Bariatric surgery

The use of bariatric surgery in the management of obesity has developed significantly over the past decade. It is now recognised that for many obese patients who fail to lose weight with lifestyle and drug interventions the risks and expense of long-term obesity outweigh those of surgery.

NICE guidelines on bariatric surgery for adults
Consider surgery for people with severe obesity if:

- They have a BMI of 40 kg/m^2 or more, or between 35 kg/ m^2 and 40 kg/ m^2 and other significant disease (e.g T2DM, hypertension) that could be improved if lost weight.
- All appropriate non-surgical measures have failed to achieve or maintain adequate clinically beneficial weight loss for at least 6 months
- They are receiving or will receive intensive specialist management
- They are generally fit for anaesthesia and surgery
- They commit to the need for long-term follow-up
- Consider surgery as a first-line option for adults with a BMI of more than 50 kg/ m^2 in whom surgical intervention is considered appropriate.
- Consider orlistat before surgery if the waiting time is long

Types of bariatric surgery:

- Primarily restrictive: laparoscopic-adjustable gastric banding (LAGB) or sleeve gastrectomy
- Primarily malabsorptive: classic biliopancreatic diversion (BPD) has now largely been replaced by biliopancreatic diversion with duodenal switch
- Mixed: Roux-en-Y gastric bypass surgery

Which operation?

- LAGB produces less weight loss than malabsorptive or mixed procedures but as it has fewer complications it is normally the first-line intervention in patients with a BMI of 30-39kg/ m^2
- Patients with a BMI > 40 kg/ m^2 may be considered for a gastric bypass or sleeve gastrectomy. The latter may be done as a sole procedure or as an initial procedure prior to bypass
- Primarily malabsorptive procedures are usually reserved for very obese patients (e.g. BMI > 60 kg/ m^2)

Obesity: physiology:

Obesity hormones

- Leptin ↓ appetite
- Ghrelin ↑ appetite

Thyroxine ↑ appetite but not in obese pt.

Leptin is thought to play a key role in the regulation of body weight. It is produced by adipose tissue and acts on satiety centres in the hypothalamus to ↓ appetite. More adipose tissue (e.g. in obesity) results in high leptin levels. Leptin stimulates the release of melanocyte-stimulating hormone (MSH) and corticotrophin-releasing hormone (CRH). Low levels of leptin stimulates the release of neuropeptide Y (NPY)

Ghrelin Where as leptin induces satiety, ghrelin stimulates hunger. It is produced mainly by the fundus of the stomach and the pancreas. Ghrelin levels ↑ before meals and ↓ after meals

Glycaemic index (GI) describes the capacity of a food to raise blood glucose in normal glucose-tolerant individuals. Foods with a high GI may be associated with ↑ risk of obesity and the post-prandial hyperglycemia associated with such foods may also ↑ the risk of T2DM

High GI	White rice (87), baked potato (85), white bread (70), corn flakes, rice krispies, watermelon, croissants, extruded breakfast cereals, straight glucose (100)
Medium GI	Couscous (65), boiled new potato (62), digestive biscuit (59), basmati rice (58), whole wheat products, sweet potato, table sugar, most white rices (e.g. jasmine)
Low GI	Fruit and vegetables (except potatoes, watermelon), peanuts, grainy breads, pasta, legumes/pulses, milk, products extremely low in carbohydrates (fish, eggs, meat, some cheeses, nuts, cooking oil), brown rice

Hypercholesterolemia rather than hypertriglyceridemia: nephrotic syndrome, cholestasis, hypothyroidism

Hyperlipidemia: causes of predominantly hypertriglyceridemia (secondary causes):

- Diabetes Mellitus (types 1 and 2)
- Obesity
- Alcohol
- Chronic renal failure
- Drugs: thiazides, non-selective β-blockers, unopposed estrogen
- Liver disease

Remnant hyperlipidemia

Overview

- Rare cause of mixed hyperlipidemia (**raised cholesterol and triglyceride levels**)
- Also known as Fredrickson type III hyperlipidemia, broad-β disease and dysbetalipoproteinemia
- Associated with APO-E2 homozygosity
- High incidence of ischemic heart disease and peripheral vascular disease
- Thought to be caused by impaired removal of intermediate density lipoprotein from the circulation

Features

- Yellow palmar creases
- Palmer xanthomas
- Tuberous xanthomas

Management

- Fibrates are first line treatment

Familial hypercholesterolemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the hepatic proteins involved in clearance of LDL-cholesterol from the circulation

Clinical diagnosis is now based on the **Simon Broome criteria**:

- In adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- For definite FH: tendon xanthoma in patient or 1st or 2nd degree relatives or DNA-based evidence of FH
- For possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

Homozygous familial hypercholesterolaemia is exceedingly rare - most patients die in their teenage years from a myocardial infarction.

Management

- The use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- Referral to a specialist lipid clinic is usually required
- The maximum dose of potent statins are usually required
- First-degree relatives have a 50% chance of having the disorder and should therefore be offered screening
- Statins should be discontinued in women 3 months before conception due to the risk of congenital defects

NICE recommend increasing to simvastatin 80 mg if total cholesterol of less than 4 mmol/litre or LDL cholesterol of less than 2 mmol/litre is not attained

Primary prevention CVD: 10-year risk of 20% is cut-off

Primary prevention: a systematic strategy should be used to identify people aged 40-74 who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of 20% or greater.

The 1991 Framingham equations are still recommended to assess 10-year CVD risk. It is however recommended that adjustments are made in the following situations:

- First-degree relative with a history of premature coronary heart disease (defined as < 55 years in ♂s and < 65 years in ♀s) - ↑ risk by 1.5 times if one relative affected or up to 2.0 times if more than one relative affected
- South asian ethnicity - ↑ risk by 1.4 times

Along with lifestyle changes drug treatment should be considered for patients with a 10-year CVD risk of 20% or greater

- Simvastatin 40mg on is the first line treatment
- **There is no target level for total or LDL cholesterol for primary prevention**
- Liver function tests should be check at baseline, within 3 months and at 12 months but not again unless clinically indicated

Secondary prevention

- All patients with CVD should be taking a statin in the absence of any contraindication
- NICE recommend increasing to simvastatin 80 mg if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained

Characteristic Xanthomata In Hyperlipidemia:

In prolonged cholestasis features include: ↑ serum cholesterol, moderate ↑ in triglyceride, serum is not lipaemic, ↓ HDL levels. Clinical features include: palmar xanthomas; tuberous xanthomas (particularly on extensor surfaces); tendinous xanthomas are rare. Xanthomas usually only occur if cholestasis has persisted for more than 3 months sometimes fat deposits may involve bone and peripheral nerves.

The presence of tendon xanthomata and ↑LDL, ↑T.chol ≡ HDL meet the diagnostic criteria for familial hypercholesterolemia.

Palmar xanthoma
- **Remnant** hyperlipidemia
- May less commonly be seen in familial hypercholesterolemia

Eruptive xanthoma are due to high triglyceride levels and present as multiple red/yellow vesicles on the extensor surfaces (e.g. elbows, knees)

Causes of **eruptive** xanthoma
- Familial hyper**triglyceride**mia
- Lipoprotein lipase deficiency

Tendon **xanthoma**, tuberous xanthoma, xanthelasma
- Familial hyper**cholesterole**mia
- Remnant hyperlipidemia

Xanthelasma are also seen without lipid abnormalities

Management of xanthelasma, options include:
- Surgical excision
- Topical trichloroacetic acid
- Laser therapy
- Electrodesiccation

Flushing, diarrhea, bronchospasm, tricuspid stenosis, pellagra → carcinoid with liver mets diagnosis: urinary 5-HIAA

Hypo- not hypertension is seen in carcinoid syndrome secondary to serotonin release

Carcinoid syndrome:

- Usually occurs when metastases are present in the liver and release serotonin into the systemic circulation
- May also occur with lung carcinoid as mediators are not 'cleared' by the liver

Features
- Flushing (often earliest symptom)
- Diarrhea
- Bronchospasm
- Hypotension
- Right heart valvular stenosis (left heart can be affected in bronchial carcinoid)

- ACTH and GHRH may also be secreted resulting in, for example, cushing's syndrome
- Pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour

Investigation
- Urinary 5-HIAA
- Plasma chromogranin A y

Management
- Somatostatin analogues e.g. Octreotide
- Diarrhea: cyproheptadine may help

Primary HYPOparathyroidism is usually the first endocrine manifestation of type 1 autoimmune POLYendocrinopathy syndrome. While (MEN) → hyperparathyroidism is a common finding

Autoimmune Polyendocrinopathy Syndrome

Addison's disease (autoimmune hypoadrenalism) is associated with other endocrine deficiencies in approximately 10% of patients. There are two distinct types of autoimmune polyendocrinopathy syndrome (APS), with type 2 (sometimes referred to as Schmidt's syndrome) being much more common.

APS2 has a polygenic inheritance and is linked to HLA DR3/DR4. Patients have Addison's disease plus either:
- Type 1 diabetes mellitus
- Autoimmune thyroid disease (Hypothyroid)

- Hypogonadism
- Celiac disease
- Myasthenia gravis

APS1 is Multiple Endocrine Deficiency Autoimmune Candidiasis (MEDAC). It is a very rare autosomal recessive disorder caused by mutation of AIRE1 gene on chromosome 21

Features of APS type 1 (2 out of 3 needed)
- Chronic mucocutaneous candidiasis (typically first feature as young child)
- Addison's disease
- Primary hypoparathyroidism

Vitiligo can occur in both types

Multiple Endocrine Neoplasias: autosomal dominant inheritance.

MEN type I	MEN type IIa	MEN type IIb
Wermer Syndrome	Sipple Syndrome	
Mnemonic 'three P's': • Parathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia • Pituitary (70%) • Pancreas (50%, e.g gastrinoma) • Also: adrenal and thyroid	• Pheochromocytoma 95% • Medullary thyroid CA 70% • Parathyroid (60%)	• Medullary thyroid cancer • PHEOCHROMOCYTOMA • Marfanoid body habitus • Neuromas • Intestinal polyps (identified histologically as ganglioneromas and are usually asymptomatic)
MEN1 gene Presentation → **hypercalcemia**	RET oncogene	RET oncogene

The high incidence of parathyroid tumours and hypercalcemia make serum calcium a useful indicator of MEN type 1 in suspected individuals

In Pheochromocytoma and suspected MEN IIa
check for medually ca 1st then parathyroid (measure the calcitonin using pentagastrin)

Androgen Insensitivity Syndrome: is an **X-linked recessive** condition due to end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype. Complete androgen insensitivity syndrome is the new term for testicular feminisation syndrome

Features

- 'Primary amennorhoea'
- Undescended testes causing groin swellings
- Breast development may occur as a result of conversion of testosterone to oestradiol

Diagnosis

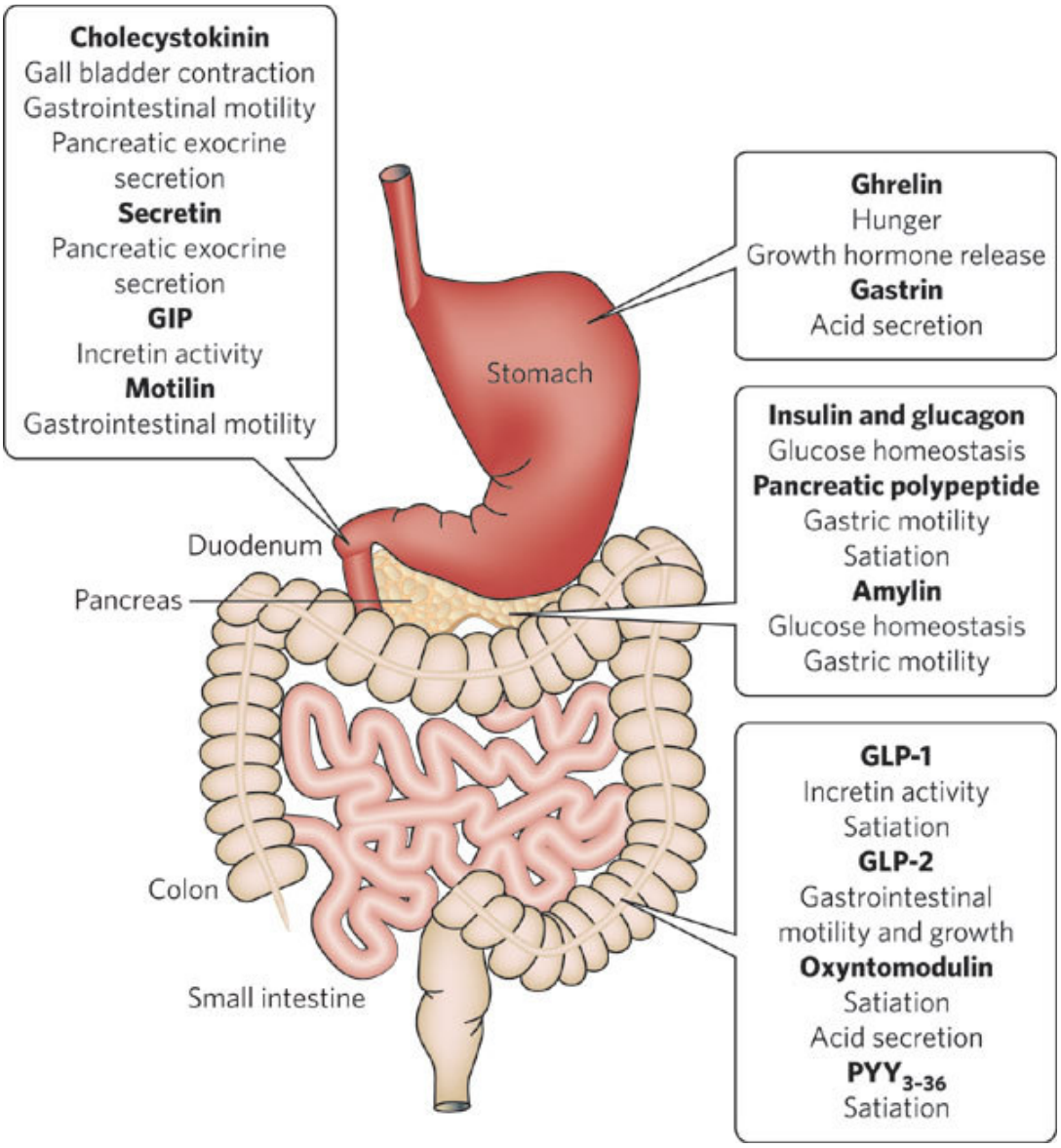
- Buccal smear or chromosomal analysis to reveal 46XY genotype

Management

- Counselling - raise child as female
- Bilateral orchidectomy (increased risk of testicular cancer due to undescended testes)
- Estrogen therapy


(c) GiggleMed.com
"WE WILL WATCH HER DIARRHEA CLOSELY"

GASTROINTISTINAL SYSTEM



Amylase: breaks starch down to sugars → Saliva + Pancreas

GI Enzymes :

The following brush border enzymes are involved in the breakdown of carbohydrates:

- Maltase: cleaves disaccharide maltose to glucose + glucose
- Sucrase: cleaves sucrose to fructose and glucose
- Lactase: cleaves disaccharide lactose to glucose + galactose

Gastrointestinal Hormones

	Source	Stimulus	Actions
Gastrin	**G** cells in antrum of the stomach	• Stomach Distension • extrinsic nerves Inhibited by: • low antral pH • somatostatin	↑ HCL= ↑acidity, pepsinogen and IF secretion, ↑ gastric motility, ↑ gastric mucosa breakdown (trophic effect)
CCK	I cells in upper small intestine	Partially digested proteins and triglycerides	↑ secretion of enzyme-rich fluid from pancreas, contraction of gallbladder and relaxation of sphincter of Oddi, ↓ gastric emptying, trophic effect on pancreatic acinar cells, induces satiety
Secretin	**S** cells in upper small intestine	Acidic chyme, fatty acids	↑ secretion of bicarbonate-rich fluid from pancreas and hepatic duct cells, ↓ gastric acid secretion, trophic effect on pancreatic acinar cells
VIP	Small intestine pancreas	Neural	Stimulates secretion by pancreas and intestines, inhibits acid and pepsinogen secretion
Somatostatin	D cells in the pancreas & stomach	Fat, bile salts and glucose in the intestinal lumen	↓ acid and pepsin secretion, ↓ gastrin secretion, ↓ pancreatic enzyme secretion, ↓ insulin and glucagon secretion inhibits trophic effects of gastrin, stimulates gastric mucous production

GI Acid Secretion Control:

Principle mediators of acid secretion

- Gastrin
- Vagal stimulation
- Histamine

Factors increasing acid secretion

- Gastrinoma
- Small bowel resection (removal of inhibition)
- Systemic mastocytosis (elevated histamine levels)
- Basophilia

Factors decreasing acid secretion

- Drugs: H2-antagonists, PPIs
- Hormones: secretin, VIP, GIP, CCK

Pharyngeal Pouch is a posteromedial diverticulum or herniation through Killian's dehiscence. Killian's dehiscence is a triangular area in the wall of the pharynx between the thyropharyngeus and cricopharyngeus muscles. It is more common in older patients and is 5 times more common in men

Features

- Dysphagia
- Regurgitation
- Aspiration
- Neck swelling which gurgles on palpation
- Halitosis (noticeably unpleasant odors exhaled in breathing)

Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhea)

Travellers' diarrhea may be defined as at least 3 loose to watery stools in 24 hours with or without one or more of abdominal cramps, fever, nausea, vomiting or blood in the stool. The most common cause is *Escherichia coli*

***Bacillus cereus* infection most commonly results from reheated rice**

Another pattern of illness is 'acute food poisoning'. This describes the sudden onset of nausea, vomiting and diarrhea after the ingestion of a toxin. Acute food poisoning is typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*.

Stereotypical histories

Escherichia coli	**Common amongst travellers** Watery stools Abdominal cramps and nausea
Giardiasis	**Prolonged**, non-bloody **diarrhea**
Cholera	Profuse, watery diarrhea Severe dehydration resulting in weight loss Not common amongst travellers
Shigella	**Bloody diarrhea** Vomiting and abdominal pain
Staphylococcus aureus	Severe vomiting **Short incubation period**
Campylobacter **Most common cause in UK**	A flu-like prodrome followed by crampy abdominal pains fever and diarrhoea which may be bloody Complications include Guillain-Barre syndrome
Bacillus cereus	Two types of illness are seen vomiting within 6 hours diarrhoeal illness occurring after 6 hours
Amoebiasis	Gradual onset bloody diarrhea abdominal pain and tenderness may last for several weeks

Incubation period

- 1-6 hrs: Staphylococcus aureus, Bacillus cereus
- 12-48 hrs: Salmonella, Escherichia coli
- 48-72 hrs: Shigella, Campylobacter
- > 7 days: Giardiasis, Amoebiasis

Clostridium difficile is a Gram positive rod often encountered in hospital practice. It produces an exotoxin which causes intestinal damage leading to a syndrome called **pseudomembranous colitis**. *Clostridium difficile* develops when the normal gut flora are suppressed by broad-spectrum antibiotics. **Clindamycin is historically associated with causing *Clostridium difficile*** but the aetiology has evolved significantly over the past 10 years. **Second and third generation cephalosporins (e.g ciprofloxacin) are now the leading cause.**

Features:

- Diarrhea
- Abdominal pain
- If severe, toxic dilatation
- Sometimes seen in nosocomial outbreaks

Diagnosis is made by detecting *Clostridium difficile* **TOXIN** (CDT) in the stool

Management:

- **ORAL** metronidazole for 10-14 days
- If severe or not responding to metronidazole then **ORAL** vancomycin may be used.
- For life-threatening infections a combination of oral vancomycin and intravenous metronidazole should be used

---

Bacterial overgrowth: the **gold standard** investigation of bacterial overgrowth is **small bowel aspiration and culture.** Important association: Systemic sclerosis, diverticulae and blind loop.

Other possible investigations include:

- Hydrogen breath test
- 14c-xylose breath test
- 14c-glycocholate breath test: used increasingly less due to low specificity

In practice many clinicians give an empirical course of antibiotics as a trial

---

Exotoxins are generally released by Gram positive bacteria with the notable exceptions of Vibrio cholerae and some strains of *E. coli*

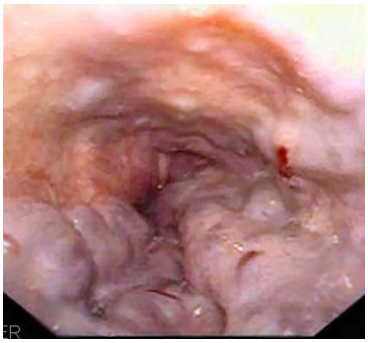
Diphtheria toxin commonly causes a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce **necrosis of myocardial, neural and renal tissue**.

Staph. aureus exotoxins lead to acute gastroenteritis, toxic shock syndrome and Staphylococcal scalded skin syndrome

Lockjaw is caused by *Clostridium tetani* neurotoxin (tetanospasmin)

Cholera toxin causes activation of adenylate cyclase leading to ↑ in cAMP levels, which in turn leads to ↑ chloride secretion.

Esophageal Varices



Acute treatment of variceal hemorrhage

- ABC: patients should ideally be resuscitated prior to endoscopy
- Correct clotting: FFP, vitamin K
- **Vasoactive agents: terlipressin is currently the only licensed vasoactive agent. It has been shown to be of benefit in initial hemostasis and preventing rebleeding. It acts by Constriction of the splanchnic vessels** (contraindicated in IHD, use Octreotide as alternative)
- Prophylactic antibiotics have been shown in multiple meta-analyses to ↓ mortality in patients with liver cirrhosis
- Endoscopy: endoscopic variceal band ligation is superior to endoscopic sclerotherapy
- Sengstaken-blakemore tube if uncontrolled hemorrhage (in urgent setting when endoscopy is not ready)
- Transjugular intrahepatic portosystemic shunt (TIPSS) if above measures fail

Prophylaxis of variceal hemorrhage

- Propranolol: ↓ rebleeding and mortality compared to placebo
- Endoscopic variceal band ligation (EVL) is superior to endoscopic sclerotherapy. It should be performed at two-weekly intervals until all varices have been eradicated. Proton pump inhibitor cover is given to prevent EVL-induced ulceration

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Barrett's Esophagus refers to the **metaplasia** of the lower esophageal mucosa, with the usual squamous epithelium being replaced by columnar epithelium. There is ↑ risk of esophageal adenocarcinoma, estimated at 50-100 folds.

Histological features: the columnar epithelium may resemble that of either the cardiac region of the stomach or that of the small intestine (e.g. with goblet cells, brush border)

Management

- Endoscopic surveillance with biopsies
- Low grade dysplasia: high-dose proton pump inhibitor for 8-12 weeks
- High grade dysplasia: surgery or cryotherapy.

GERD

24hr esophageal pH monitoring is gold standard investigation in GERD

Usually there is poor correlation between symptoms and endoscopy appearance

Indications for upper GI endoscopy:

- Age > 55 years
- Symptoms > 4 weeks or persistent symptoms despite treatment
- Dysphagia
- Relapsing symptoms
- Weight loss

If endoscopy is negative consider 24-hr esophageal pH monitoring (the gold standard test for diagnosis)

Dysphagia: The table below gives characteristic exam question features for conditions causing dysphagia:

Pain on swallowing (odynophagia) is a typical of esophageal candidiasis, a well documented complication of inhaled steroid therapy

Esophageal cancer	Dysphagia may be associated with weight loss, anorexia or vomiting during eating Past history may include Barrett's esophagus, GERD, excessive smoking or alcohol use
Oesophagitis	May be history of heartburn Odynophagia but no weight loss and systemically well
candidiasis	There may be a history of HIV or other risk factors such as steroid inhaler use
Achalasia	Dysphagia of both liquids and solids from the start Heartburn Regurgitation of food - may lead to cough, aspiration pneumonia etc
Pharyngeal pouch	More common in older men Represents a posteromedial herniation between thyropharyngeus and cricopharyngeus muscles Usually not seen but if large then a midline lump in the neck that gurgles on palpation Typical symptoms are dysphagia, regurgitation, aspiration and chronic cough. Halitosis may occasionally be seen
Systemic sclerosis	Other features of CREST syndrome may be present, namely Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia
Myasthenia gravis	Other symptoms may include extraocular muscle weakness or ptosis Dysphagia with liquids as well as solids
Globus hystericus	May be history of anxiety Symptoms are often intermittent

Achalasia: Failure of esophageal peristalsis and of relaxation of lower esophageal sphincter (LOS) due to degenerative loss of ganglia from Auerbach's plexus i.e. LOS contracted, esophagus above dilated. Achalasia typically presents in middle-age and is more common in women

Dysphagia affecting both solids and liquids from the start - think achalasia

Clinical features

- Dysphagia of BOTH liquids and solids
- Typically variation in severity of symptoms
- Heartburn
- Regurgitation of food - may lead to cough, aspiration pneumonia etc
- Malignant change in small number of patients
- 7% ↑ in risk of squamous cell carcinoma

The gold standard test for achalasia is esophageal manometry

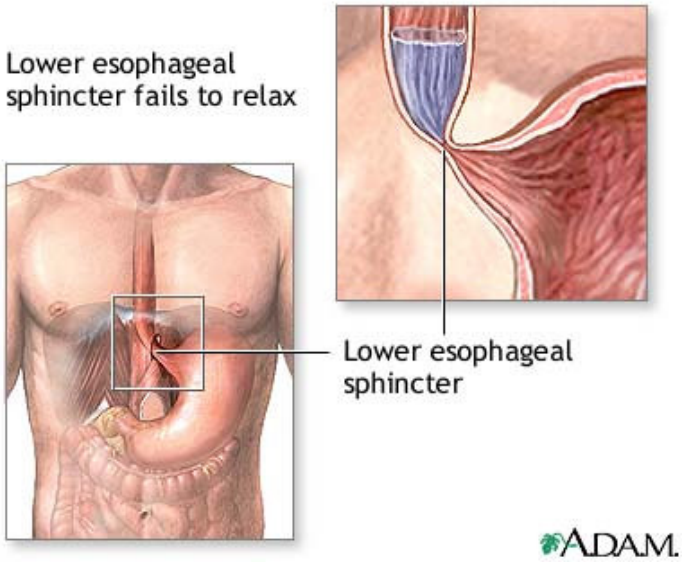
Disease	Achalasia	Scleroderma
Manometery finding	Loss of peristalsis in distal esophagus, failure of LOS to relax during swallowing and (i.e **↑ residual relaxing pressure**)	Loss of peristalsis in distal esophagus BUT **↓ resting LOS pressure**

Investigations

- Manometry: excessive LOS tone which doesn't relax on swallowing - considered most important diagnostic test
- Barium swallow shows grossly expanded esophagus, fluid level
- CXR: wide mediastinum, fluid level

Treatment

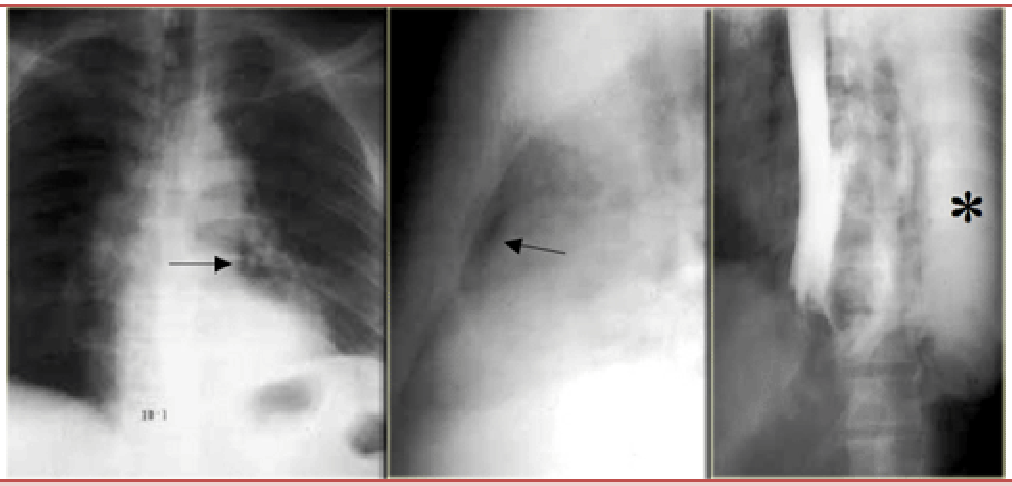
- Intra-sphincteric injection of botulinum toxin
- Heller cardiomyotomy
- Balloon dilation
- Drug therapy has a role but is limited by side-effects



Boerhaave's syndrome: it is rupture of the esophageal wall, relatively uncommon but serious and potentially fatal condition.

Features:

- Complete transmural (full-thickness) laceration or perforation of the esophagus, distinct from **Mallory-Weiss syndrome, a nontransmural esophageal tear also associated with vomiting**.
- Perforation is almost always on **Left** side of **Lower** esophagus.
- Gastric contents enter the mediastinum and pleural cavity, if one were to perform a pleural fluid aspirate; one is likely to aspirate gastric contents!
- ♂ > ♀ and typically between 50-70 years old
- Other clinical features that may suggest the diagnosis include odynophagia and surgical emphysema in the neck



Chest radiographs show pneumomediastinum (arrows).
Esophagram with extravasated water soluble contrast material in left hemithorax (star)

Causes:

- Vomiting (against a closed glottis) in eating disorders such as bulimia
- Rarely: Extremely forceful coughing - Obstruction by food

Diagnosis:

- Radiographs show mediastinal gas, effusion, and later pneumothorax.
  Esophagram is used to confirm leak, first with water-soluble contrast, then barium if no leak demonstrated.

Management: Early operation after appropriate resuscitation offers the best chance of survival.

Iatrogenic perforation, accounts for 85-90% of cases of esophageal rupture, typically as a complication of an endoscopic procedure, feeding tube, or unrelated surgery.

Dyspepsia:

Causes

- NSAIDs
- Bisphosphonates
- Steroids

The following drugs may cause reflux by reducing lower esophageal sphincter (LOS) pressure

- Calcium channel blockers*
- Nitrates*
- Theophyllines

*calcium channel blockers and nitrates are occasionally used in the management of achalasia, itself a cause of dyspepsia, because of their effect on the LOS.

In 2004 NICE published guidelines for the management of dyspepsia in primary care. These take into account the age of the patient (younger or older than 55 years) and the presence or absence of 'alarm signs':

- Chronic gastrointestinal bleeding
- Progressive unintentional weight loss
- Progressive difficulty swallowing
- Persistent vomiting
- Iron deficiency anemia
- Epigastric mass
- Suspicious barium meal

Deciding whether urgent referral for endoscopy is needed

Urgent referral (within 2 weeks) is indicated for patients with any alarm signs irrespective of age. Routine endoscopic investigation of patients of any age, presenting with dyspepsia and without alarm signs is not necessary, however patients aged 55 years and over should be referred urgently for endoscopy if dyspepsia symptoms are:

- Recent in onset rather than recurrent and
- Unexplained (e.g. New symptoms which cannot be explained by precipitants such as NSAIDs) and
- Persistent: continuing beyond a period that would normally be associated with self-limiting problems (e.g. Up to four to six weeks, depending on the severity of signs and symptoms)

Managing patients who do not meet referral criteria ('undiagnosed dyspepsia')

This can be summarised at a step-wise approach

- Review medications for possible causes of dyspepsia
- Lifestyle advice
- Trial of full-dose PPI for one month*
- 'Test and treat' using carbon-13 urea breath test

*it is unclear from studies whether a trial of a PPI or a 'test and treat' should be used first

Helicobacter pylori is a Gram negative bacteria associated with a variety of gastrointestinal problems, principally peptic ulcer disease

H. pylori eradication 7 day course of:

- PPI + amoxicillin + clarithromycin, or
- PPI + metronidazole + clarithromycin

Associations

- Peptic ulcer disease (95% of duodenal ulcers, 75% of gastric ulcers)
- Gastric cancer
- B cell lymphoma of MALT tissue (eradication of H pylori 80% causes regression)
- Atrophic gastritis

The role of H pylori in Gastresophageal reflux disease (GERD) is unclear - there is currently no role of eradication of H pylori in GERD.

H Pylori tests

Urea breath test - no antibiotics in past 4 weeks, no antisecretory drugs (e.g. PPI) in past 2 weeks

Urea breath test

- Patients consume a drink containing carbon isotope 13 (13C) enriched urea
- Urea is broken down by *H. pylori* urease
- After 30 mins patient exhale into a glass tube
- Mass spectrometry analysis calculates the amount of 13C CO_2
- Sensitivity 95-98%, specificity 97-98%
- Used to confirm eradication

Rapid urease test (e.g. CLO test)

- Biopsy sample is mixed with urea and pH indicator
- Color change if H pylori urease activity
- Sensitivity 90-95%, specificity 95-98%

Serum antibody

- Remains positive after eradication
- Sensitivity 85%, specificity 80%

Culture of gastric biopsy

- Provide information on antibiotic sensitivity
- Sensitivity 70%, **specificity 100%**

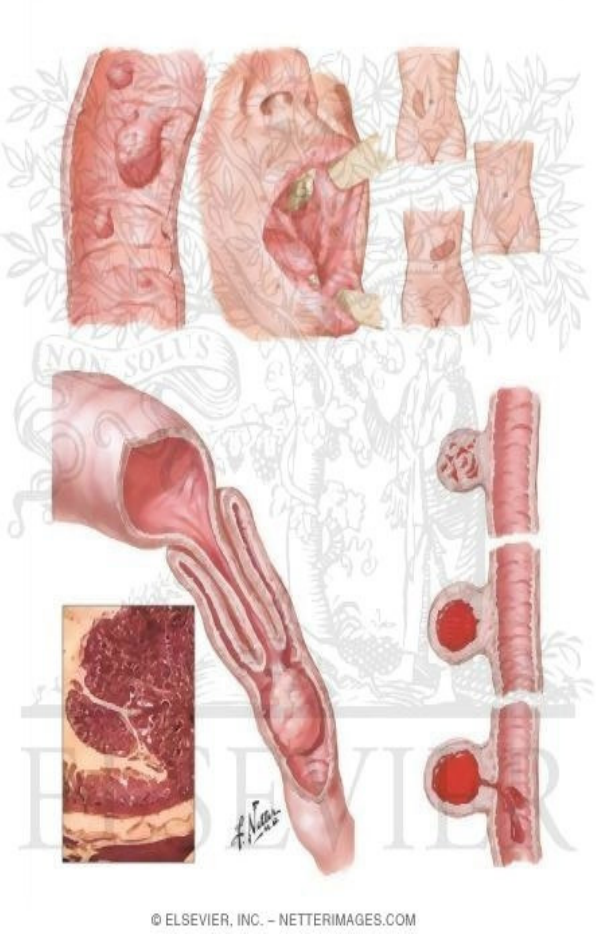
Gastric biopsy

- Histological evaluation alone, no culture
- **Sensitivity** 95-**99%**, specificity 95-99%

Stool antigen test

- Sensitivity 90%, specificity 95%

Peutz-Jeghers syndrome is an autosomal dominant condition characterized by numerous hamartomatous polyps in the gastrointestinal tract. It is also associated with **pigmented freckles on the lips, face, palms and soles**. Around 50% of patients will have died from a gastrointestinal tract cancer by the age of 60 years. and it is unusual to find cases in young adults without the characteristic peristomal hyperpigmentation



Genetics

- Autosomal dominant
- Responsible gene encodes serine threonine kinase LKB1 or STK11

Features

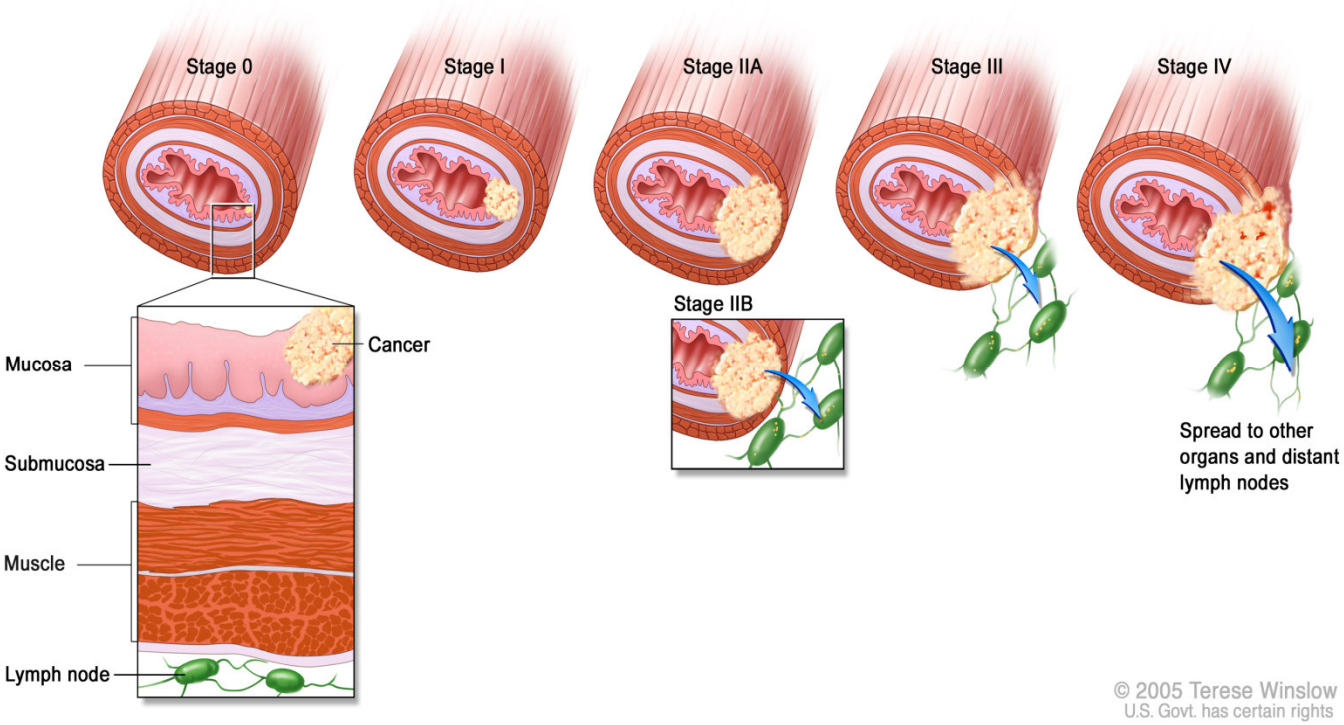
- Hamartomatous polyps in GI tract (mainly small bowel)
- Pigmented lesions on lips, oral mucosa, face, palms and soles
- classical histological appearance of smooth muscle "**arborisation**"
- Intestinal obstruction e.g. Intussusception
- Gastrointestinal bleeding

Management

- Conservative unless complications develop

Esophageal Cancer Until recent time esophageal cancer was most commonly due to a squamous cell carcinoma but the incidence of adenocarcinoma is rising rapidly. **Adenocarcinoma is now (since 2010) the most common type of oesophageal cancer** and is more likely to develop in patients with a history of gastro-esophageal reflux disease (GERD) or Barrett's.
The majority of tumours are in the middle third of the esophagus.

***Helicobacter pylori* may actually be protective against esophageal cancer**



Risk factors:

• Smoking • Alcohol • Achalasia • Plummer-vinson syndrome • Rare: coeliac disease, scleroderma • Sensetive to radiotherapy	Squamous Cell Carcinoma
• GERD • Barrett's esophagus	Adenocarcinoma

Gastric adenocarcinoma - signet ring cells

Gastric cancer

Epidemiology

- Overall incidence is decreasing, but incidence of tumors arising from the cardia is increasing
- Peak age = 70-80 years
- More common in Japan, China, Finland and Columbia than the west
- More common in ♂s, 2:1

Associations

- H. pylori infection (although it is protective against esophageal cancer)
- **Blood group A**: g**A**stric c**A**ncer
- Gastric adenomatous polyps
- Pernicious anemia
- Smoking
- Diet: salty, spicy, nitrates
- May be negatively associated with duodenal ulcer

Investigation

- Diagnosis: endoscopy with biopsy
- Staging: CT or endoscopic ultrasound - **endoscopic ultrasound has recently been shown to be superior to CT**

Colorectal cancer:

Screening:

- Most cancers develop from adenomatous polyps therefore a screening program could theoretically ↓ mortality
- Main techniques being evaluated are faecal occult blood (FOB) testing, sigmoidoscopy and colonoscopy
- Fecal occult blood testing is the only method to have been proven to ↓ mortality (by about 20%) in trials. Sensitivity can be ↑ by DNA analysis for the APC gene
- Trials looking at screening using flexible sigmoidoscopy are currently underway
- Carcinoembryonic antigen may be used to **monitor for recurrence in patients post-operatively or to assess response to treatment in patients with metastatic disease**. The CEA-scan study is a nuclear medicine procedure — that uses a small dose of radioactive isotope to image tumors sometimes invisible to other diagnostic tests. That isotope is guided to tumors via antibody fragments engineered to seek out and attach to any tissue that expresses carcinoembryonic antigen (CEA), a protein found on virtually all colorectal tumors. CEA blood tests attempt to detect this same protein in blood, but often fail to do so, due to lack of sensitivity.

Causes for a positive fecal occult blood testing are:

- 2-10%: cancer (colorectal cancer, gastric cancer)
- 20-30% adenoma or polyps
- Bleeding peptic ulcer
- Angiodysplasia of the colon

Staging and Grading:

- The Dukes staging system is widely employed for classifying colorectal cancers and is a useful predictor of survival. Tumour grade and depth of penetration are also important:
- Duke A (Stage I) defines a tumour confined to the bowel wall (i.e. mucosa and submucosa).
- Duke B (Stage II) invades through the muscle wall.
- Duke C (Stage III) involves lymph nodes.
- After this the patient presents with metastatic disease at distant sites (Stage IV).

Prognostic indicators post complete resection includes:

- Poorly differentiated histological type.
- Tumour adherence to adjacent organs.
- Bowel perforation.
- Colonic obstruction at the time of diagnosis.
- Venous invasion by the tumour.

Management:

- Surgical excision of a colonic carcinoma is the main treatment
- Adjuvant chemotherapy (5-fluorouracil and folinic acid) is warranted in high-risk stage II

colonic carcinomas and all stage III colonic carcinomas.

- The addition of oxaliplatin has been shown to improve survival in these patients in a large multicentre trial (MOSAIC study), but the additional drug can cause a severe peripheral neuropathy.
- Adjuvant radiotherapy is used in rectal carcinomas. This is combined with chemotherapy in stage II and III rectal carcinomas to reduce the risk of local as well as metastatic relapse.

Genetics:

It is currently thought there are three types of colon cancer:

- Sporadic (95%)
- Hereditary non-polyposis colorectal carcinoma (HNPCC, 5%)
- Familial adenomatous polyposis (FAP, <1%)

Studies have shown that sporadic colon cancer may be due to a series of genetic mutations. For example, more than half of colon cancers show allelic loss of the adenomatous polyposis coli (APC) gene. It is believed a further series of gene abnormalities e.g. activation of the K-ras oncogene, deletion of p53 and DCC tumour suppressor genes lead to invasive carcinoma

HNPCC, an autosomal dominant condition, is the most common form of inherited colon cancer. Around 90% of patients develop cancers, often of the proximal colon, which are often poorly differentiated and highly aggressive. Currently four gene mutations have been identified (including in the hMLH1 and hMSH2 genes). The Amsterdam criteria are sometimes used to aid diagnosis:

Amsterdam criteria for HNPCC

- At least 3 family members with colon cancer
- The cases span at least two generations
- At least one case diagnosed before the age of 50 years

HNPCC screening for ↑ risk group:

- Colonoscopy every 2 years from 20 to 40 years age then annually
- Check mutation in DNA or mismatched repair gene.

Familial Adenomatous Polyposis (FAP) is a rare autosomal dominant condition which leads to the formation of hundreds of polyps by the age of 30-40 years. Patients inevitably develop carcinoma. It is due to a mutation in a tumour suppressor gene called adenomatous polyposis coli gene (APC), located on chromosome 5. Genetic testing can be done by **analysing DNA from** a patient's **white blood cell**. Patients generally have a total colectomy with ileo-anal pouch formation in their twenties.

Patients with FAP are also at risk from duodenal tumours which is important cause of death.

A variant of FAP called Gardner's syndrome can also feature osteomas of the skull and mandible, can be identified based on oral findings, including multiple impacted and supernumerary teeth, multiple jaw osteomas which give a "cotton-wool" appearance to the jaws, as well as multiple odontomas, Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE), in addition to multiple adenomatous polyps of the colon, thyroid carcinoma and epidermoid cysts on the skin.

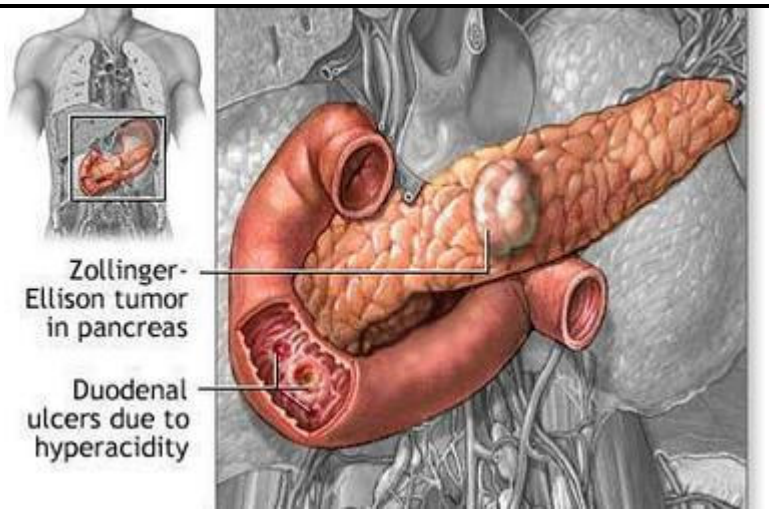
NICE recommend the following patients are **referred urgently** (i.e. within 2 weeks) to colorectal services for investigation:

- Patients > 40 years old, reporting rectal bleeding with a change of bowel habit towards looser stools and/or ↑ stool frequency persisting for 6 weeks or more
- Patients > 60 years old, with rectal bleeding persisting for 6 weeks or more without a change in bowel habit and without anal symptoms
- Patients > 60 years old, with a change in bowel habit to looser stools and/or more frequent stools persisting for 6 weeks or more without rectal bleeding
- Any patient presenting with a right lower abdominal mass consistent with involvement of the large bowel
- Any patient with a palpable rectal mass
- **Unexplained iron deficiency anemia in men or non-menstruating women (Hb < 11 g/dl in men, < 10 g/dl in women)**

Zollinger-Ellison Syndrome

is condition characterized by excessive levels of gastrin, usually from a gastrin secreting tumour usually of the duodenum or pancreas. Around 30% occur as part of MEN type I syndrome

Zollinger-Ellison syndrome typically presents with multiple gastroduodenal ulcers causing **abdominal pain, diarrhea and malabsorption**. High-dose proton pump inhibitors are needed to control the symptoms.



Zollinger-Ellison syndrome: epigastric pain and diarrhea

Diagnosis

- Fasting gastrin levels, the single best screen test: done in 3 different days as the gastrin secretion is pulsatile
- Secretin stimulation test: considered +ve if there is ↑ in gastrin >200 pg/mL after secretin injection (Normally Secretin supresses gastrin, but in ZE, it simply shows that the source of gastrin is not the stomach and it is somewhere else like pancresae)

Management:

- If not mets, surgical resection is the cure
- Octreotide can be used to alleviate symptoms with interferon and chemotherapy to attempt cure non respectable tumor
- PPI is used to control symptoms in actute stages

Gastric MALT Lymphoma

- Associated with *H. pylori* infection in 95% of cases
- Good prognosis
- If low grade then 80% respond to *H. pylori* eradication
- Paraproteinemia may be present

VIPoma

VIP (vasoactive intestinal peptide)

- Source: small intestine, pancreas
- Stimulation: neural
- Actions: stimulates secretion by pancreas and intestines, inhibits acid and pepsinogen secretion

VIPoma

- 90% arise from pancreas
- Large volume diarrhea (secretory type due to enterocytes stimulatioin)
- Weight loss
- Dehydration
- Hypokalemia, hypochlorhydria (refers to states where the production of gastric acid is low)

Angiodysplasia is a vascular deformity of the gastrointestinal tract which predisposes to bleeding and iron deficiency anemia. It is associated with aortic stenosis

Angiodysplasia is associated with aortic stenosis

The association between angiodysplasia and aortic stenosis is thought to be caused by von Willebrand factor (vWF) being proteolysed in the turbulent blood flow around the aortic valve. vWF is most active in vascular beds with high shear stress, such as angiodysplasia, and deficiency of vWF increases the bleeding risk from such lesions

Diagnosis

- Colonoscopy
- Mesenteric angiography if acutely bleeding

Management

- Endoscopic cautery or argon plasma coagulation
- Antifibrinolytics e.g. Tranexamic acid
- Estrogens may also be used

Acute Pancreatitis: The vast majority of cases in the UK are caused by gallstones and alcohol

Popular mnemonic is **GET SMASHED**

- **G**allstones
- **E**thanol
- **T**rauma
- **S**teroids
- **M**umps (other viruses include Coxsackie B)
- **A**utoimmune (e.g. Polyarteritis nodosa), **A**scaris infection
- **S**corpion venom
- **H**ypertriglyceridemia, **H**yperchylomicronemia**, **H**ypercalcemia, **H**ypothermia
- **E**RCP
- **D**rugs (azathioprine, mesalazine*, didanosine, bendroflumethiazide, furosemide, pentamidine, steroids, sodium valproate)
- ↑ **D**egree burn of large skin area with significant inhalation injury

Rare features associated with pancreatitis include:

- Ischemic (Purtscher) retinopathy (cotton wool spots seen on fundoscopy) - may cause temporary or permanent blindness. This condition may be seen following head trauma and in conditions such as acute pancreatitis, fat embolisation, amniotic fluid embolisation, and vasculitic diseases.

Poor prognostic factors (Ranson's criteria):

- Age > 55
- WBC > 16
- Urea > 16
- Glucose > 11
- Alb < 30
- ALT > 250
- $Ca^{+} < 1$
- LDH > 350
- $PO_2 < 8$
- Hematocrit ↓ >10%
- Base deficit > 4
- Fluid loss > 6L

CRP is now a widely used marker of severity in acute pancreatitis. Other methods which have to correlate with prognosis include the Ranson criteria and APACHE II score (Acute Physiology And Chronic Health Evaluation). Pancreatitis in the context of HIV infection may be secondary to anti-retroviral treatment (especially didanosine) or by opportunistic infections e.g. CMV

*pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine
**Hyperchylomicronemia may be caused by hereditary lipoprotein lipase deficiency and apolipoprotein CII deficiency. It predisposes to recurrent attacks of acute pancreatitis

Chronic Pancreatitis

Chronic Pancreatitis is an inflammatory condition which can ultimately affect both the exocrine and endocrine functions of the pancreas. Around 80% of cases are due to alcohol excess with up to 20% of cases being unexplained.

Features of chronic pancreatitis:

- Pain is typically worse 15 to 30 minutes following a meal
- Steatorrhoea: symptoms of pancreatic insufficiency usually develop between 5 and 25 years after the onset of pain
- Diabetes mellitus develops in the majority of patients. It typically occurs more than 20 years after symptom begin

Investigation

- Abdominal x-ray shows pancreatic calcification in 30% of cases
- CT is more sensitive at detecting pancreatic calcification
- Functional tests: pancreolauryl and Lundh tests may be used to assess exocrine function if imaging inconclusive

Management

- Pancreatic enzyme supplements
- Analgesia
- Antioxidants: limited evidence base - one study suggests benefit in early disease

Pancreatic Cysts and Pseudocysts:

Pseudocysts: are uncommon complication of acute pancreatitis and are localised collections of pancreatic fluid and debris, usually in the lesser sac. They are initially contained within a fragile wall of granulation tissue which eventually forms a fibrous capsule.

Diagnosis: they cannot be diagnosed until more than 6 weeks after the acute attack, and may present with:

- Abdominal pain or a mass.
- Fever
- Persistently raised amylase and liver function tests.

Management:

- Small pseudocysts usually resolve spontaneously
- > 6cm in diameter seldom disappear spontaneously and may lead to complications such as hemorrhage and infection. They are usually managed by endoscopic or percutanous drainage or surgical intervention.

Cysts: Cystic tumour can occur in the pancreas. There are two main types:

- Serous cystadenoma: benign and remain benign.
- Mucinous cystadenoma: this may be benign but has the potential to become malignant.

Diagnosis:

- CT or MRI can distinguish between the two.
- Aspiration of the cyst for cytology and carcinogenic embryonic antigen.

Management:

- Mucinous neoplasm: most patients undergo limited surgery of the pancreatic cyst.
- Serous cystadenoma or aymptomatic pseudocyst: can also be associated with polycystic kidney disease and von Hippel–Lindau disease. Considerable debate exists as to whether follow up is necessary; in younger patients it may not be. Anyhow, guidelines generally recommend annual review for a period of around 4 years.

Pancreatic Cancer:

Epidemiology and general points:

- Incidence in the West: 9 cases per 100 000 and it's increasing over the last 20 years.
- 60% are ♂
- 5-year survival rate: 2%
- K-ras is the most common oncogene in this condition
- Insulinomas are the commonest form of endocrine tumours of the pancreas
- Majority of cases occur in patients over the age of 60

Associations

- Smoking (with a twofold increase in incidence)
- Diabetes
- Chronic pancreatitis
- Hereditary pancreatitis
- Hereditary non-polyposis colorectal carcinoma
- Multiple endocrine neoplasia
- Peutz-jeghers syndrome
- BRCA2
- Dysplastic naevus syndrome

Diagnosis:

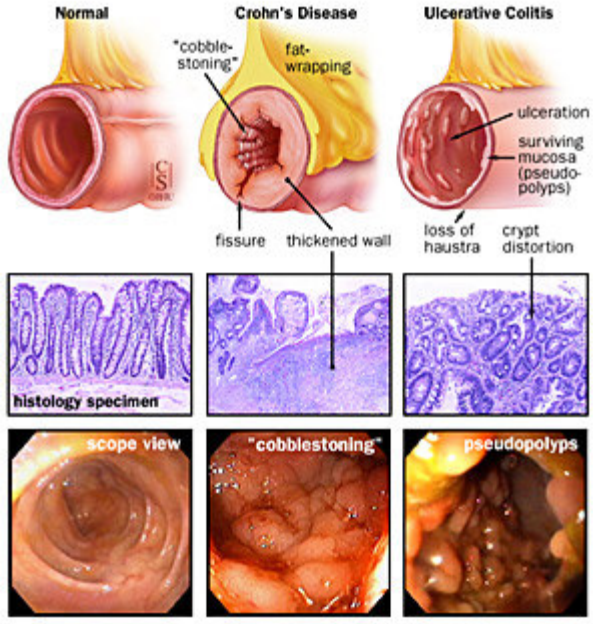
- Contrast CT is used for diagnosis and assessment of invasion
- ERCP restricted to palliative care
- CA 19-9
- U/S abdomen is less reliable when the tumor is in the body or tail

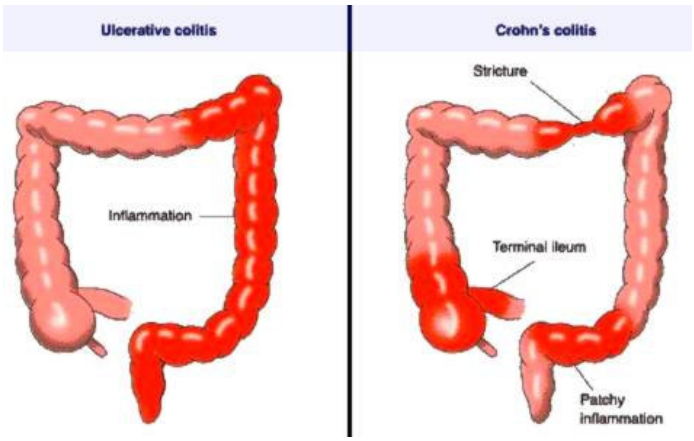
Management

- Surgical intervention represents the only chance of long-term survival with < 20% suitable for surgery at diagnosis. Eligibility for resection depend on:
    - Tumor size < 4cm
    - Invasion of superior mesenteric artery or portal vein
    - Presence of mets
- Radio and chemotherapy are ineffective

Cowden's syndrome is an inherited condition resulting from a defect in the PTEN tumour suppressor gene. Hamartomatous polyps of the GI tract are often the first manifestation along with characteristic muco-cuteneous lesions such as oral mucosal papillomas, palmoplantar keratoses and trichilemmomas (benign tumours of hair follicles). The syndrome is important to diagnose early because of the high risk of malignancy, particularly of the breast and thyroid. Thyroid dysfunction is common even in the absence of cancer.

Familial juvenile polyposis also results in multiple polyps in the colon identical to those found in Cowden's syndrome but the associated oral lesions are absent.





Malabsorption is characterized by diarrhea, steatorrhoea and weight loss. Causes:

Intestinal	Pancreatic	Biliary	Other
• Coeliac disease • Crohn's disease • Tropical sprue • Whipple's • Giardiasis • Brush border enzyme deficiencies (e.g. ↓ Lactase)	• Chronic pancreatitis • Cystic fibrosis • Pancreatic cancer	• Biliary obstruction • Primary biliary cirrhosis	• Bacterial overgrowth (e.g. Systemic sclerosis, diverticulae, blind loop) • Short bowel syndrome • Lymphoma

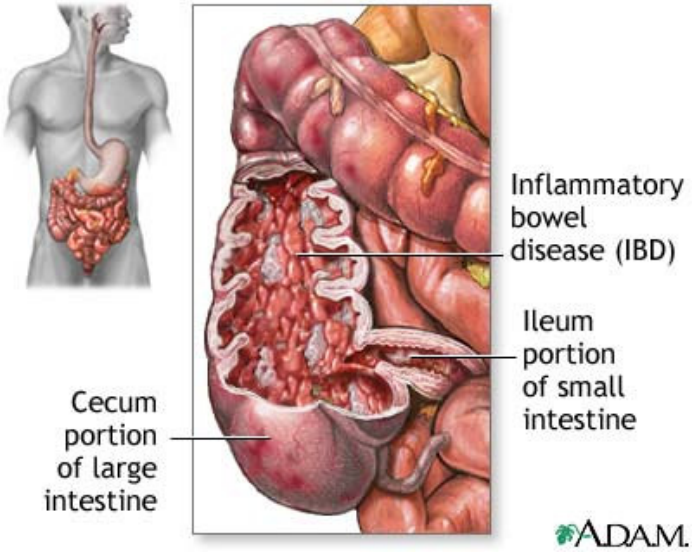
IBD: The histological differences between ulcerative colitis and Crohn's are summarised below:

	Ulcerative colitis (UC)	Crohn's disease (CD)
Features	• Bloody diarrhoea more common • Abdominal pain in the left lower quadrant • Tenesmus	• Diarrhoea usually non-bloody • Weight loss more prominent • Upper GI symptoms, mouth ulcers, perianal disease • Abdominal mass palpable in the right iliac fossa
Extra-intestinal	• Primary sclerosing cholangitis	
Complications	• Risk of colorectal cancer high in UC than CD	• Obstruction, fistula, colorectal cancer
Pathology	• Inflammation always starts at rectum and never spreads beyond ileocaecal valve • Continuous disease • Associated with pANCA antigen	• Lesions may be seen anywhere from the mouth to anus • Skip lesions may be present • Associated with ASCA (**A**nti-*S**accharomyces* **C**erevisiae* **A**ntibodies
Histology	• No inflammation beyond submucosa (unless fulminant disease) - inflammatory cell infiltrate in lamina propria • neutrophils migrate through the walls of glands to form crypt abscesses • depletion of goblet cells and mucin from gland epithelium	• Inflammation in all layers from mucosa to serosa • goblet cells • granulomas
Endoscopy	• Widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')	• Deep ulcers, skip lesions
Radiology	**Barium enema** • loss of haustrations • superficial ulceration, 'pseudopolyps' • long standing disease: colon is narrow and short -'drainpipe colon'	**Small bowel enema** • high sensitivity and specificity for examination of the terminal ileum • strictures: 'Kantor's string sign' • proximal bowel dilation • 'rose thorn' ulcers • fistulae

DON'T GIVE ANTI-DIARRHEAL Rx FOR ACUTE COLLITIS → TOXIC MEGACOLON

Ulcerative Colitis

Treatment can be divided into inducing and maintaining remission



Inducing remission

- Treatment depends on the extent and severity of disease
- Rectal aminosalicylates or steroids: for distal colitis rectal mesalazine has been shown to be superior to rectal steroids
- Oral aminosalicylates or steroids
- Severe colitis should be referred to hospital

Maintaining remission

- Oral aminosalicylates e.g. Mesalazine

Patients with concomitant UC and PSC are at ↑ risk of developing colonic cancer, and it is recommended that they be screened annually with colonoscopy.

Patients with extensive UC should be screened 8 to10 years from the onset of symptoms. Colonoscopy should be performed:

- 3-yearly in the second decade
- 2-yearly in the third decade
- Yearly by the fourth decade.

Patients post-liver transplant for PSC still should have yearly screening. Each case should be considered for the benefits and risks of the colonoscopy.

Criteria to determine **colitis severity** include:

- Stool frequency >6/day
- ESR > 30 mm/hr
- HR > 90 bpm
- Temp > 37.8°C in 2 out of 4 days
- Anemia (Hb <75% predicted)

In severe ulcerative colitis, patients should be treated with intravenous treatments including steroids, fluids, subcutaneous heparin and elemental diet. The patient should also have daily examination and monitoring including review by surgeons, blood tests, stool chart, heart rate, temperature and abdominal X-rays.

Ulcerative Colitis and colorectal cancer

Overview

- Risk of colorectal cancer is 10-20 times that of general population
- The ↑ risk mainly related to chronic infection
- Worse prognosis than patients without ulcerative colitis (partly due to delayed diagnosis)
- Lesions may be multifocal

Factors increasing **risk of cancer**

- Disease duration > 10 years
- Patients with pancolitis
- Onset before 15 years old
- Unremitting disease
- Poor compliance to treatment

Crypt abscesses are sometimes seen in Crohn's disease but they are more commonly associated with ulcerative colitis

Crohn's disease is a form of inflammatory bowel disease. It commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus

- Bloods
  - C-reactive protein correlates well with disease activity
- Endoscopy
  - Colonoscopy is the investigation of choice
  - Features suggest of crohn's include deep ulcers, skip lesions
- Histology
  - Inflammation in all layers from mucosa to serosa
  - Goblet cells
  - Granulomas
- Small bowel enema
  - High sensitivity and specificity for examination of the terminal ileum
  - Strictures: 'kantor's string sign'
  - Proximal bowel dilation
  - 'Rose thorn' ulcers
  - Fistulae

General points

- Patients should be strongly advised to stop smoking
- Some studies suggest an ↑ risk of relapse secondary to NSAIDs and the combined oral contraceptive pill but the evidence is patchy

Active disease

- Mesalazine: whilst evidence base is limited widely used in active disease
- Steroids (oral, topical or intravenous)
- Azathioprine is used as a second-line treatment in active disease
- Mercaptopurine (also called 6-mercaptopurine, 6-MP)
- Methotrexate is used in patients intolerant of azathioprine or refractory disease. Usually given intramuscularly, but not effective in maintaining remission. Significant anemia is a contra-indication for methotrexate.
- Infliximab is useful in refractory disease and fistulating crohn's. Patients typically continue on azathioprine or methotrexate

Perianal disease: Metronidazole is first-line

Enteral feeding

- May be used in addition to or instead of other measures to induce remission

Surgery

- Around 80% of patients with Crohn's disease will eventually have surgery

Whipple's disease is a rare multi-system disorder caused by *Tropheryma whippelii* infection. It is more common in those who are HLA-B27 positive and in middle-aged men

Features

- Malabsorption: diarrhea, weight loss
- Large-joint arthralgia (seronegative arthropathy)
- Lymphadenopathy
- Skin: hyperpigmentation and photosensitivity
- Pleurisy, pericarditis
- Neurological symptoms (rare): ophthalmoplegia, dementia, seizures, ataxia, myoclonus

Investigation

- Jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules
- ↑ CRP and ESR
- Hypoalbuminemia

Management

- Varies e.g. IV penicillin then oral co-trimoxazole for a year

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Microscopic colitis: is defined by the triad of:

1. Watery diarrhea
2. Normal colonoscopy
3. ↑ Inflamation of the lamina propria of the colon.

This disease includes collagenous and lymphocytic colitis. It is an uncommon disease with an incidence of 5/100,000 per year and frequents the elderly (mean age 55-68) and women.

Association:

- NSAIDs
- Omeprazole, Lansoprazole
- Ticlopidine
- Cimetidine

Treatment: includes just stopping the offending medication. Corticosteroids, cholestyramine and now bismuth have been used as treatment with some effect. Recurrence however, does occur.

Irritable bowel syndrome (IBS): NICE published clinical guidelines on the diagnosis and management of irritable bowel syndrome (IBS) in 2008

The diagnosis of IBS should be considered if the patient has had the following for at least 6 months:

- Abdominal pain, and/or
- Bloating, and/or
- Change in bowel habit

A positive diagnosis of IBS should be made is the patient has abdominal pain relieved by defecation or associated with altered bowel frequency stool form, in addition to 2 of the following 4 symptoms:

- Altered stool passage (straining, urgency, incomplete evacuation)
- Abdominal bloating (more common in women than men), distension, tension or hardness
- Symptoms made worse by eating
- Passage of mucus

Features such as lethargy, nausea, backache and bladder symptoms may also support the diagnosis

Red flag features should be enquired about:
- Rectal bleeding
- Unexplained/unintentional weight loss
- Family history of bowel or ovarian cancer
- Onset after 60 years of age

Suggested primary care **investigations** are:
- Full blood count
- ESR
- CRP
- Coeliac disease screen (antiendomysial antibodies or tissue transglutaminase)

The management of irritable bowel syndrome (IBS) is often difficult and varies considerably between patients. NICE issued guidelines in 2008

First-line pharmacological treatment - according to predominant symptom
- Pain: antispasmodic agents
- Constipation: laxatives but avoid lactulose
- Diarrhea: loperamide is first-line

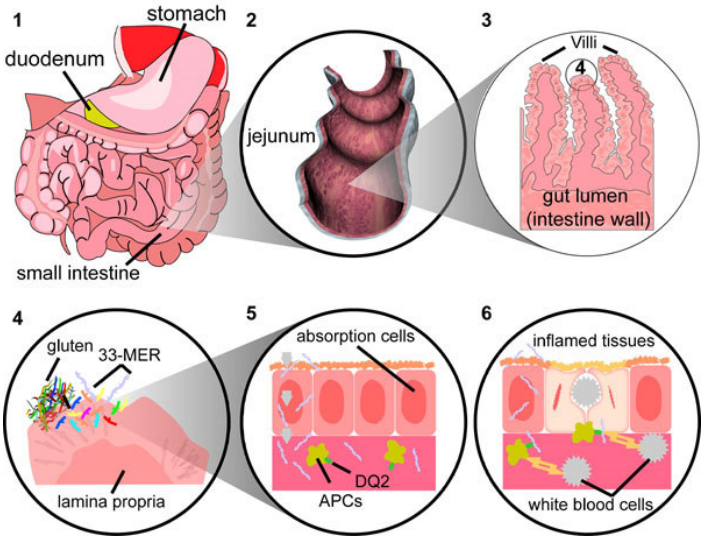
Second-line pharmacological treatment
- low-dose tricyclic antidepressants (e.g. amitriptyline 5-10 mg) are used in preference to selective serotonin reuptake inhibitors

Other management options
- Psychological interventions - if symptoms do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (refractory IBS), consider referring for cognitive behavioural therapy, hypnotherapy or psychological therapy
- Complementary and alternative medicines: 'do not encourage use of acupuncture or reflexology for the treatment of IBS'

General dietary advice
- Have regular meals and take time to eat
- Avoid missing meals or leaving long gaps between eating
- Drink at least 8 cups of fluid per day, especially water or other non-caffeinated drinks such as herbal teas
- Restrict tea and coffee to 3 cups per day
- ↓ intake of alcohol and fizzy drinks
- Consider limiting intake of high-fibre food (for example, wholemeal or high-fibre flour and breads, cereals high in bran, and whole grains such as brown rice)
- ↓ intake of 'resistant starch' often found in processed foods

- Limit fresh fruit to 3 portions per day
- For diarrhea, avoid sorbitol
- For wind and bloating consider increasing intake of oats (for example, oat-based breakfast cereal or porridge) and linseeds (up to one tablespoon per day).

Coeliac Disease: is caused by sensitivity to the protein gluten. Repeated exposure leads to villous atrophy which in turn causes malabsorption. Conditions associated with coeliac disease include dermatitis herpetiformis (a vesicular, pruritic skin eruption) and autoimmune disorders (type 1 diabetes mellitus and autoimmune hepatitis). It is strongly associated with HLA-DQ2 (95% of patients) and HLA-B8 (80%) as well as HLA-DR3 and HLA-DR7



The management of coeliac disease involves a gluten-free diet. Gluten containing cereals include:

- Wheat: bread, pasta, pastry
- Barley*: beer
- Rye
- Oats**

Some notable foods which are gluten-free include:

- Rice
- Potatoes
- Corn (maize)

*whisky is made using malted barley. Proteins such as gluten are however removed during the distillation process making it safe to drink for patients with coeliac disease
**some patients with coeliac disease appear able to tolerate oats

In 2009 NICE issued guidelines on the investigation of coeliac disease, they suggest that the following patients should be screened for coeliac disease:

Signs and symptoms	Conditions
? Chronic or intermittent diarrhea ? Failure to thrive or faltering growth (in children) ? Persistent or unexplained gastrointestinal symptoms including nausea and vomiting **? Prolonged fatigue ('tired all the time')** ? Recurrent abdominal pain, cramping or distension ? Sudden or unexpected weight loss ? Unexplained iron-deficiency anemia, or other unspecified anemia ? Recurrent mouth ulcers	? Autoimmune thyroid disease ? Dermatitis herpetiformis ? Irritable bowel syndrome ? Type 1 diabetes ? First-degree relatives (parents, siblings or children) with coeliac disease

Complications

- Anemia: iron, folate and vitamin B12 deficiency (**folate deficiency is more common** than vitamin B12 deficiency in coeliac disease)
- Hyposplenism
- Osteoporosis
- Lactose intolerance
- Enteropathy-associated T-cell lymphoma of small intestine
- Subfertility, unfavourable pregnancy outcomes
- Rare: esophageal cancer, other malignancies

Diagnosis is made by a combination of **immunology and jejunal biopsy**. Villous atrophy and immunology normally reverses on a gluten-free diet.

NICE issued guidelines on the investigation of coeliac disease in 2009. If patients are already taking a gluten-free diet they should be asked, if possible, to reintroduce gluten for at least 6 weeks prior to testing.

Immunology

- Tissue transglutaminase (TTG) antibodies (IgA) are first-choice according to NICE
- Endomyseal antibody (IgA)
- Anti-gliadin antibody (IgA or IgG) tests are **NOT** recommended by NICE
- Anti-casein antibodies are also found in some patients

Jejunal biopsy

- Villous atrophy
- Crypt hyperplasia
- ↑ in intraepithelial lymphocytes
- Lamina propria infiltration with lymphocytes

Rectal gluten challenge has been described but is not widely used

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Tropical Sprue: this disease is most common in the Carribbean and the Far-East. It is characterized by a picture of small intestinal malabsorption and the cause is thought to be infectious in origin.

Diagnosis:

- Jejunal biopsy reveals:
  - Mild villous atrophy
  - ↑ villous crypts
  - Mononuclear cellular infiltrates
  - Enlarged epithelial cells
  - Large nuclei caused by folate and/or vitamin B12 deficiency.

Treatment:

- Tetracyclines 250mg qds up to 6 months
- Ampicillin may be used as an alternative in patients who are intolerant of tetracyclines.
- Folate and B12 deficiencies should also be corrected
- Complete recovery is possible with appropriate therapy.

Jejunal Villous Atrophy: whilst coeliac disease is the classic cause of jejunal villous atrophy there are a number of other causes you need to be aware of:

- Coeliac disease
- Tropical sprue
- Hypogammaglobulinemia
- Gastrointestinal lymphoma
- Whipple's disease
- Cow's milk intolerance

Toxic Megacolon: usually ssociated with severe colitis (criteria mentioned above). The colon is dilated when it is measured > 5.5cm.

Management:

- Toxic dilatation can be treated medically for 12-24 hours with IV and rectal hydrocortisone but if there is then no improvement in the triad of
    - Pulse
    - Stool frequency
    - Colon dilatation

  } Then:
- Patient should undergo an urgent colectomy. Otherwise, there is an increased risk of perforation, which has a mortality of 30%.
- In addition to steroids, the acutely unwell patient should receive:
    - K^+ supplementation
    - Thromboembolism prophylaxis.
- Antibiotics have not been demonstrated to help

Short Bowel Syndrome: in patients who have removal of more than one-half of the small intestine, malabsorption syndrome may result. It may occur in patients with Crohn's disease or those with ischemic bowel who have undergone significant bowel resection.

Presentation:

- Diarrhoea
- Steatorrhoea
- Malabsorption manifestation: Weight loss, anemia, osteoporosis/osteomalacia, electrolyte disturbances and hypovolemia.

Management:

- In patients with > 100cm of jejunum, oral intake is still possible. Diarrhoea may reduce with lactose exclusion or with a course of metronidazole to eradicate bacterial overgrowth.
- In patients with < 100cm of jejunum, total parenteral nutrition is recommended.

Melanosis coli is a disorder of pigmentation of the bowel wall. Histology demonstrates pigment-laden macrophages. It is associated with laxative abuse, especially anthraquinone compounds such as senna

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Spontaneous bacterial peritonitis (SBP) is a form of peritonitis usually seen in patients with ascites secondary to liver cirrhosis.

Diagnosis

- Paracentesis: neutrophil count > 250 cells/ul

Management

- Intravenous cefotaxime is usually given
- Patients who have had an episode of SBP should be on prophylactic antibiotics

Alcoholic liver disease is a marker of poor prognosis in SBP.

Ascites:

Old Classification

Transudate (protein < 30g/l) causes:	**Exudate** (protein > 30g/l) causes:
• Cirrhosis and portal hypertension • Nephrotic syndrome • Cardiac failure • Budd–Chiari syndrome • Myxodema.	• Intra-abdominal tuberculosis • Pancreatitis. • Hepatic or peritoneal malignancy

However the serum-ascites albumin gradient (SAAG) has now largely replaced this concept and is the **best single test for classifying ascites** into portal hypertensive (SAAG >1.1 g/dL) and non–portal hypertensive (SAAG <1.1 g/dL) causes. The terms high-albumin gradient and low-albumin gradient should replace the terms transudative and exudative in the description of ascites

New Classification

↑ **SAAG (>1.1 g/dL)** causes:	↓ **SAGG (<1.1 g/dL)** causes:
• Cirrhosis • Alcoholic hepatitis • Schistosomiasis • Fulminant hepatic failure • Budd–Chiari syndrome • Acute or chronic portal vein obstruction • Cardiac diseases • Spontaneous bacterial peritonitis secondary to cirrhosis.	• Nephrotic syndrome • Protein losing enteropathy • Peritoneal carcinomatosis • Tuberculous peritonitis • Pancreatic duct leak • Biliary ascites.

Liver function tests (LFTs) Interpretation:

- Bilirubin:
  - Bilirubin is derived from the breakdown of heme in the red blood cells within the reticuloendothelial system.
  - The unconjugated bilirubin then binds albumin and is taken up by the liver.
  - In the liver it is conjugated which then makes it water-soluble and thus allows it to be excreted into the urine.
  - Normally total serum bilirubin is measured; however, the unconjugated (indirect bilirubin) and conjugated (direct bilirubin) portions can be.

- Albumin - sensitive marker of hepatic function, but not useful in the acute stages as it has a long half life (20 days).

- Total protein.

- Transferases - usually *either* alanine aminotransferase (ALT) or aspartate aminotransferase (AST); rarely does a laboratory routinely provide both:
  - These enzymes normally reside inside cells (in cytoplasm) so raised levels usually represent hepatocellular damage. A**L**T is more specific to the **L**iver, as AST is also found in cardiac and skeletal muscle and red blood cells.
  - Very high levels (>1000 IU/L) suggest drug-induced hepatitis (e.g. paracetamol), acute viral hepatitis (A or B), ischemic, or rarely, autoimmune hepatitis.
  - The ratio of AST to ALT can give some extra clues as to the cause:
    - In chronic **L**iver disease A**L**T >AST, once cirrhosis established AST >ALT
    - The extremes of the ratio of AST:ALT can also be helpful:
      - >2 suggests alcoholic liver disease.
      - <1.0 suggests nonalcoholic liver disease.

- Gamma-glutamyltransferase (GGT) - also related to the bile ducts. Typically elevated in cholestasis (with elevated ALP) but, if ALP normal, suggests induction of hepatic metabolic enzymes (e.g alcohol or enzyme-inducing drugs).

- Alkaline phosphatase (ALP) - comes mainly from the cells lining bile ducts but also in bone. Marked elevation is typical of cholestasis (often with elevated GGT) or bone disorders (usually normal GGT). Isoenzyme analysis may help identify source. It is physiologically increased when there is increased bone turnover (e.g. adolescence) and is elevated in the third trimester of pregnancy (produced by the placenta).

When Bilirubin is elevated and it's mentioned that no bilirubin in uring dipstick
↓
Unconjugated Bilirubin

As unconjugated bilirubin is not soluble in water hence can't appear in urine

Hepatomegaly common causes:

- Cirrhosis: if early disease, but later liver ↓ in size. Associated with a non-tender, firm liver
- Malignancy: metastatic spread or primary hepatoma. Associated with a hard, irregular. Liver edge
- Right heart failure: firm, smooth, tender liver edge. May be pulsatile

Hepatomegaly + dupuytren's contracture + parotitis are associated with alcoholic liver disease

Other causes

- Abscess: pyogenic, amoebic
- Glandular fever
- Hematological malignancies
- Hemochromatosis
- Hydatid disease
- Malaria
- Primary biliary cirrhosis
- Sarcoidosis, amyloidosis
- Viral hepatitis

Causes of hepatosplenomegaly

- Chronic liver disease* with portal hypertension
- Infections: glandular fever, malaria, hepatitis
- Lymphoproliferative disorders
- Myeloproliferative disorders e.g. CML
- Amyloidosis

*the latter stages of cirrhosis are associated with a small liver

Primary Biliary Cirrhosis is chronic liver disorder typically seen in middle-aged ♀s (♀:♂ ratio of 9:1). The aetiology is not fully understood although it is thought to be an autoimmune condition, with HLA DR3 association. Interlobular bile ducts become damaged by a chronic inflammatory process causing progressive cholestasis, which may eventually progress to cirrhosis. The classic presentation is **itching in a middle-aged woman**

Associations (Remember ... it's thought to be an autoimmune condition)

- Sjogren's syndrome (seen in up to 80% of patients)
- Rheumatoid arthritis
- Systemic sclerosis
- Thyroid disease
- Membranous GN
- RTA

Clinical features

- Early: may be asymptomatic (e.g. **Raised ALP** on routine LFTs) or fatigue, pruritus
- **Cholestatic jaundice**
- Hyperpigmentation, especially over pressure points
- Xanthelasmas, xanthomata
- Also: clubbing, hepatosplenomegaly
- Late: may progress to liver failure

Diagnosis

- Anti-mitochondrial antibodies (AMA) M2 subtype in 98% of patients and are highly specific.
- Smooth muscle antibodies in 30% of patients
- Raised serum IgM

Management

- Median survival is 7-10 yrs, but ↓ to 2 yrs if jaundice is present
- Pruritus: **cholestyramine**
- Fat-soluble vitamin supplementation
- Ursodeoxycholic acid
- Liver transplantation e.g. If bilirubin > 100 (PBC is a major indication) - recurrence in graft can occur but is not usually a problem. 5 yr survival post transplant 80%

> Primary biliary cirrhosis - the **M** rule
> - Ig**M**
> - Anti-**M**itochondrial antibodies, **M**2 subtype
> - **M**iddle aged ♀s

Complications

- Malabsorption: osteomalacia, coagulopathy
- Sicca syndrome (Sjögren's syndrome) occurs in 70% of cases
- Portal hypertension: ascites, variceal hemorrhage
- Hepatocellular cancer (20-fold ↑ risk)

Primary sclerosing cholangitis is a biliary disease of unknown aetiology characterized by inflammation and fibrosis of intra and extra-hepatic bile ducts

Associations

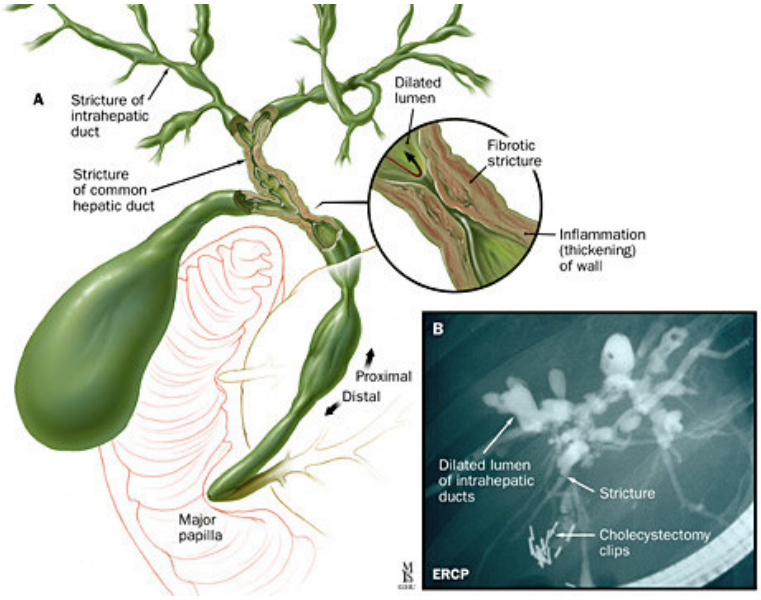
- Ulcerative colitis: 4% of patients with UC have PSC, 80% of patients with PSC have UC
- Crohn's (much less common association than UC)
- HIV

Features

- Cholestasis
- Hepatomegaly
- Intermittent jaundice

Investigation

- ERCP is the standard diagnostic tool, showing multiple biliary strictures giving a 'beaded' appearance
- MRCP is superior to ERCP
- ANCA may be positive
- There is a limited role for liver biopsy, which may show fibrous, obliterative cholangitis often described as 'onion skin'



Complications

- Cholangiocarcinoma (in 10%)
- ↑ risk of colorectal cancer

Management:

- Liver transplantation, survival post transplant is 90% although rejection is high. Indication for transplantation:
  - Bilirubin > 100 µmol/l
  - Recurrent bacterial cholangitis
  - Ascitis
  - Refractory itching
  - Cholangiocarcinoma is a contraindication for transplantation

The most common cause of biliary disease in patients with HIV is sclerosing cholangitis due to infections such as CMV, Cryptosporidium and Microsporidia

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Wilson's Disease is an autosomal recessive disorder characterized by excessive copper deposition in the tissues. Metabolic abnormalities include ↑ copper absorption from the small intestine and ↓ hepatic copper excretion. Wilson's disease is caused by a defect in the ATP7B gene located on chromosome 13.

The onset of symptoms is usually between 10 - 25 years. Children usually present with liver disease whereas the first sign of disease in young adults is often neurological disease

Features result from excessive copper deposition in the tissues, especially the brain, liver and cornea:

- Liver: hepatitis, cirrhosis
- Neurological: speech and behavioral problems are often the first manifestations. Also: tremor, chorea
- Kayser-fleischer rings →
- Renal tubular acidosis (esp. Fanconi syndrome)
- Hemolysis
- Blue nails

Combination of parkinsonism + chronic liver disease in young patient

Diagnosis

- ↓ serum ceruloplasmin
- ↑ 24hr urinary copper excretion
- Slit lamp: Kayser-Fleischer ring

Management

- D-penicillamine: chelates copper 1.5-2g/day in divided dose then 0.75-1.5g/day maintenance
- Trientine
- Zinc

Gilbert's syndrome is an autosomal recessive* condition of defective bilirubin conjugation due to a deficiency of UDP glucuronyl transferase. The prevalence is approximately 1-2% in the general population. Viral infections are common triggers for a rise in the bilirubin in patients with Gilbert's

Features

- **Isolated hyperbilirubinemia**
- Unconjugated hyperbilirubinemia (i.e. Not in urine)
- Jaundice may only be seen during an intercurrent illness

Investigation and management

- Investigation: rise in bilirubin following prolonged fasting or IV nicotinic acid
- No treatment required

*the exact mode of inheritance is still a matter of debate

Hyperbilirubinemia
Normal dipsticks urinalysis excludes Dubin-Johnson and Rotor syndrome as these both produce a conjugated bilirubinemia.

Dubin-Johnson syndrome is a benign autosomal recessive disorder resulting in hyperbilirubinemia (conjugated, therefore present in urine). It is due to a defect in the canalicular multispecific organic anion transporter (cMOAT) protein. This causes defective hepatic bilirubin excretion.

Features:

- ↑ of conjugated
- NO elevation of liver enzymes (ALT, AST).
- Usually asymptomatic but may be diagnosed in early infancy based on laboratory tests.
- Liver biopsy shows dark granules in the hepatocytes (thought to be due to melanin deposition)
- Prognosis is good, and treatment of this syndrome is usually unnecessary. Most patients are asymptomatic and have normal life spans.

Rotor syndrome: is a rare, relatively benign autosomal recessive bilirubin disorder of unknown origin. It is a distinct disorder, yet similar to Dubin-Johnson Syndrome — both diseases cause an increase in conjugated bilirubin.

It can be differentiated from Dubin-Johnson syndrome in the following ways:

	Rotor syndrome	DJS
Appearance of liver	Normal	Liver has black pigmentation
Gallbladder	Visualized by oral holecystogram	Cannot be visualized
Urine coproporphyrin	↑ with <70% being isomer 1	Normal with >80% being isomer 1
	(Normal urine contains more of isomer 3 than isomer 1)	

Crigler-Najjar Syndrome: (CNS) is a rare disorder affecting the metabolism of bilirubin, which results in high levels of unconjugated bilirubin and often leads to brain damage in infants.

This syndrome is divided type I and type II, with the latter sometimes called Arias syndrome. These two types, along with Gilbert's syndrome, Dubin-Johnson syndrome, and Rotor syndrome, make up the five known hereditary defects in bilirubin metabolism. Unlike Gilbert's syndrome, only a few hundred

cases of CNS are known. Type I is usually fatal while only type II can survive to adult life. The syndrome is treated by liver transplantation.

Bile Acid Malabsorption:

is a cause of chronic diarrhea. It can result from malabsorption secondary to gastro-intestinal disease or be a primary disorder. Treatment with bile acid sequestrants is often effective.

Types:

- Type 1: Bile acid malabsorption, secondary to ileal resection, or ileal inflammation (e.g. in Crohn's disease)
- Type 2: Idiopathic bile acid malabsorption, Primary bile acid diarrhea
- Type 3: Secondary to various gastrointestinal diseases including cholecystectomy, vagotomy, small intestinal bacterial overgrowth, radiation enteropathy, celiac disease, chronic pancreatitis, etc.

Diagnosis:

- SeHCAT test (selenium homocholic acid taurine or tauroselcholic acid): nuclear test involves two scans a week apart and only very limited radiation exposure. Retention of SeHCAT at 7 days is normally above 15%. Values less than 15% predict a response to bile acid sequestrants. The SeHCAT test measures multiple cycles of bile acid excretion and reabsorption over 7 days. This test is not licensed in the USA, and is underutilized even where it is available
- Fecal bile acid quantfication or the 14C-glycocholic breath test are no longer in routine clinical use.

Hepatitis B:

Basics

- Incubation period (weeks) = 6-20
- Double-stranded DNA virus
- Spread: body fluids + vertical
- Chronic disease in 5-10%
- Vaccination available

Immunization

- Contains HBsAg adsorbed onto aluminum hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology
- Most schedules give 3 doses of the vaccine with a recommendation for a one-off booster 5 years following the initial primary vaccination
- At risk groups who should be vaccinated include: healthcare workers, intravenous drug users, sex workers, close family contacts of an individual with hepatitis B, individuals receiving blood transfusions regularly, chronic kidney disease patients who may soon require renal replacement therapy, prisoners, chronic liver disease patients
- Around 10-15% of adults fail to respond or respond poorly to 3 doses of the vaccine. Risk factors include age over 40 years, obesity, smoking, alcohol excess and immunosuppression
- Testing for anti-HBs is only recommended for those at risk of occupational exposure (i.e. Healthcare workers) and patients with chronic kidney disease. In these patients anti-HBs levels should be checked 1-4 months after primary immunization. The table below shows how to interpret anti-HBs levels:

Anti-HBs level (mIU/ml)	Response
> 100	Indicates adequate response, no further testing required. Should still receive booster at 5 years
10 - 100	Suboptimal response - one additional vaccine dose should be given. If immunocompetent no further testing is required
< 10	Non-responder. Test for past or previous infection. Give further vaccine course (i.e. 3 doses again) with testing following. If still fails to respond then HBIG would be required for protection if exposed to the virus

Complications

- Chronic infection (5-10%)
- Fulminant liver failure (1%)
- Hepatocellular carcinoma
- GBS
- Glomerulonephritis (memberanoproliferative)
- Polyarteritis nodosa
- Cryoglobulinemia (more with Hepa C than Hepa B)

Management:

- Pegylated interferon-alpha used to be the only treatment available. It reduces viral replication in up to 30% of chronic carriers. A better response is predicted by being ♀ < 50 years old, low HBV DNA levels, non-Asian, HIV negative, high degree of inflammation on liver biopsy
- However due to the side-effects of pegylated interferon it is now used less commonly in clinical practice. Oral antiviral medication is increasingly used with an aim to suppress viral replication (not in the dissimilar way to treating HIV patients)
- Examples include lamivudine, tenofovir and entecavir

Treatment of Hepa B is based on:

- Abnormal ALT in at least 1 occasion
- Liver biopsy shows fibrosis
- Hepa B viremia $>10^5$ HBV DNA copies per mL

Serology is a dying art form which still occurs at regular intervals in medical exams. It is important to remember a few key facts:

- Surface antigen (HBsAg) is the first marker to appear and causes the production of anti-HBs
- HBsAg normally implies acute disease (present for 1-6 months)
- If HBsAg is present for > 6 months then this implies chronic disease
- Anti-HBs implies immunity (either exposure or immunization)
- Anti-HBc implies previous (or current) infection. IgM anti-HBc appears during acute or recent hepatitis B infection and is present for about 6 months (c=current or recent)
- HBeAg results from breakdown of core antigen from infected liver cells as is therefore a marker of infectivity (e=infectivity)

Example results

- Previous immunization: anti-HBs positive, all others negative
- Previous hepatitis B (> 6 months ago), not a carrier: anti-HBc positive, HBsAg negative
- Previous hepatitis B, now a carrier: anti-HBc positive, HBsAg positive

Hepatitis B and pregnancy

- All pregnant women are offered screening for hepatitis B
- Babies born to mothers who are chronically infected with hepatitis B or to mothers who've had acute hepatitis B during pregnancy should receive a complete course of vaccination + hepatitis B immunoglobulin
- Studies are currently evaluating the role of oral antiviral treatment (e.g. Lamivudine) in the latter part of pregnancy
- There is little evidence to suggest caesarean section reduces vertical transmission rates
- Hepatitis B cannot be transmitted via breastfeeding (in contrast to HIV)

Hepatitis C is likely to become a significant public health problem in the UK in the next decade. It is thought around 200,000 people are chronically infected with the virus. At risk groups include intravenous drug users and patients who received a blood transfusion prior to 1991 (e.g. hemophiliacs). Hepa C is an RNA virus.

Transmission

- Risk of transmission during a needle stick injury is about 2%
- The risk of transmitting the virus during sexual intercourse is probably less than 5%
- Vertical transmission rate from mother to child is about 6% (high viral load at delivery ↑ risk)
- Breast feeding is not contraindicated in mothers with Hepatitis C

Features

- After exposure to the Hepatitis C virus less than 20% of patients develop an acute hepatitis

Complications

- Chronic infection (80-85%) - only 15-20% of patients will clear the virus and will hence the majority will develop chronic hepatitis C
- Cirrhosis (20-30% of those with chronic disease)
- Hepatocellular cancer
- Cryoglobulinemia

Management

- Currently a combination of interferon-α (S/C) and ribavirin (PO) are used
- Amantadine is a useful alternative for ribavirin and interferon in case if adverse effects.
- Genotype 2 and 3 respond to Rx while genotype 4 has less responsiveness.
- Genotype 3a on PCR is indication for chronic infection; it is more likely to respond to Rx.

Complications of treatment

- Ribavirin - side-effects: hemolytic anemia, cough. Women should not become pregnant within 6 months of stopping ribavirin as it is teratogenic
- Interferon α - side-effects: **flu-like symptoms, depression**, fatigue, leucopenia, thrombocytopenia

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Autoimmune hepatitis is condition of unknown etiology which is most commonly seen in young ♀s. Recognized associations include other autoimmune disorders, hypergammaglobulinemia and HLA B8, DR3. Three types of autoimmune hepatitis have been characterized according to the types of circulating antibodies present

Type I	Type II	Type III
Anti-nuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA)	Anti-liver/kidney microsomal type 1 antibodies (LKM1)	Soluble liver-kidney antigen
Affects both adults and children	Affects children only	Affects middle-age adult
		> 60% remission with steroids but relapse is 80% Azathioprine is an alternative

combination of deranged LFTs combined with secondary amenorrhea in a young female strongly suggest autoimmune hepatitis

Features

- May present with signs of chronic liver disease
- Acute hepatitis: fever, jaundice etc (only 25% present in this way)
- Amenorrhea (common)
- ANA/SMA/LKM1 antibodies, raised IgG levels
- Liver biopsy: inflammation extending beyond limiting plate **'piecemeal necrosis'**, bridging necrosis

Management

- Steroids, other immunosuppressants e.g. Azathioprine
- Liver transplantation

Alcoholic Hepatitis: commonly occurs after a prolonged period of alcohol abuse or return to alcohol after period of abstinence.

Features:

- Increased serum transaminase
- Macrocytosis
- Thrombocytopenia
- Poor hepatic synthetic function
- Leucocytosis irrespective of infection
- Increased acute phase reactants.
- **AST/ALT is usually > 2**.
- Liver enzymes do not exceed 500.

Malnutrition, jaundice, fluid retention and encephalopathy are associated with poor outlook. The discriminant function (DF) can be used to identify patients for treatment. Those who have DF > 32 have 1 month mortality rate of 50%, they may benefit from corticosteroids or pentoxyfilline. Histology can help to confirm diagnosis.

DF= 4.6 x (PT – control) + bilirubin (mg/dl)

Zieve's Syndrome: occurs in patients with excessive alcohol consumption with hemolysis and severe hyperlipidemia, abdominal pain, transient mildly raised bilirubin. It usually occurs in males and resolves once alcohol consumption is stopped.

Non-alcoholic fatty liver disease (NAFLD)

is now the most common cause of liver disease in the developed world. It is largely caused by obesity and describes a spectrum of disease ranging from:

- Steatosis - fat in the liver
- Steatohepatitis - fat with inflammation, non-alcoholic steatohepatitis (NASH), see below
- Progressive disease may cause fibrosis and liver cirrhosis

NAFLD is thought to represent the hepatic manifestation of the metabolic syndrome and hence insulin resistance is thought to be the key mechanism leading to steatosis

Non-alcoholic steatohepatitis (NASH) is a term used to describe liver changes similar to those seen in alcoholic hepatitis in the absence of a history of alcohol abuse. It is relatively common and though to affect around 3-4% of the general population. The progression of disease in patients with NASH may be responsible for a proportion of patients previously labeled as cryptogenic cirrhosis.

Obese T2DM with abnormal LFTs - ? Non-alcoholic fatty liver disease

Associated factors

- Obesity
- Hyperlipidemia
- T2DM
- Jejunoileal bypass
- Sudden weight loss/starvation

Features

- Usually asymptomatic
- Hepatomegaly
- ALT is typically greater than AST
- Increased echogenicity on ultrasound

Management

- The mainstay of treatment is lifestyle changes (particularly weight loss) and monitoring
- There is ongoing research into the role of gastric banding and insulin-sensitizing drugs (e.g. Metformin)

Liver Cirrhosis:

- Micronodular cirrhosis is associated with alcohol liver disease.
- Macronodular cirrhosis is associated with chronic hepatitis.
- Granuloma formation is not classically seen in cirrhosis.

The Child-Pugh classification is a scoring system to assess the severity of liver cirrhosis

Score	Normal	1	2	3
Bilirubin (µmol/l)	5-17	<34	34-50	>50
Albumin (g/l)	36-52	>35	28-35	<28
Prothrombin time, prolonged by (s)	12-15	<4	4-6	>6
Encephalopathy	-	none	mild	marked
Ascites	-	none	mild	marked

Summation of the scores allows the severity to be graded either A, B or C:

- < 7 = A
- 7-9 = B
- > 9 = C

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the third most common cause of cancer worldwide. Chronic hepatitis B is the most common cause of HCC worldwide with chronic hepatitis C being the most common cause in Europe.

The main risk factor for developing HCC is liver cirrhosis, for example secondary* to hepatitis B & C, alcohol, hemochromatosis and primary biliary cirrhosis.

Other **risk factors** include:

- Alpha-1 antitrypsin deficiency
- Hereditary tyrosinosis
- Glycogen storage disease
- Aflatoxin
- Drugs: oral contraceptive pill, anabolic steroids
- Porphyria cutanea tarda
- ♂ sex
- Diabetes mellitus, metabolic syndrome

Features

- Tends to present late
- Features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly
- Possible presentation is decompensation in a patient with chronic liver disease

Screening with ultrasound (+/- alpha-fetoprotein) should be considered for high risk groups such as:

- Patients liver cirrhosis secondary to hepatitis B & C or hemochromatosis
- Men with liver cirrhosis secondary to alcohol

Management options

- Early disease: surgical resection
- Liver transplantation
- Radiofrequency ablation
- Transarterial chemoembolisation
- Sorafenib: a multikinase inhibitor

*Wilson's disease is an exception

Liver biopsy:

Contraindications to percutaneous liver biopsy

- Deranged clotting (e.g. INR > 1.4)
- Low platelets (e.g. < 60 * 10^9/l)
- Anemia
- Bile duct obstruction
- Hydatid cyst
- Hemoangioma
- Uncooperative patient
- Ascites

Pyogenic liver abscess:

Management

- Drainage (needle aspiration or catheter) should always be performed
- Amoxicillin + ciprofloxacin + metronidazole
- If penicillin allergic: ciprofloxacin + clindamycin

Hepatorenal Syndrome (HRS): refers to the development of acute renal failure in a patient who has advanced liver disease, who has no identifiable cause of intrinsic renal disease. It usually represents the end-stage of a sequence of reductions in renal perfusion induced by increasingly severe hepatic injury. Splanchnic vasodilatation appears to play an important role in the decline in renal function in hepatic disease.

Diagnostic criteria have been proposed for the hepatorenal syndrome:

1. Chronic or acute hepatic disease with advanced hepatic failure and portal hypertension
2. Creatinine > 133 mmol/l that progresses over days to weeks
3. Absence of any other apparent cause for the renal disease, including shock, active sepsis, current nephrotoxic drugs, and the absence of ultrasonographic evidence of obstruction or parenchymal renal disease. It is particularly important to exclude spontaneous bacterial peritonitis, which is complicated with acute renal failure
4. Urine sodium < 10 meq/l (off diuretics) and protein excretion < 500 mg/day
5. Lack of improvement in renal function after volume expansion with 1.5litres of isotonic saline.

Hepatorenal syndrome has been categorized into two **types**:

Type 1 HRS	Type 2 HRS
• Rapidly progressive • Doubling of serum creatinine to > 221 µmol/L or a halving of the creatinine clearance to less than 20 ml/min over a period of less than 2 weeks • Very poor prognosis	•Slowly progressive •Prognosis poor, but patients may live for longer

Management: is notoriously difficult. The ideal treatment is liver transplantation but patients are often too unwell to have surgery and there is a shortage of donors. Management options:

- Vasopressin analogues, for example terlipressin, have a growing evidence base supporting their use. They work by causing vasoconstriction of the splanchnic circulation
- Volume expansion with 20% albumin
- Transjugular intrahepatic portosystemic shunt

Comon GI Surgical Problems in MRCP

Anal fissures are longitudinal or elliptical tears of the squamous lining of the distal anal canal. If present for less than 6 weeks they are defined as acute, and chronic if present for more than 6 weeks. Around 90% of anal fissures occur on the posterior midline

Management of an **acute** anal fissure (< 6 weeks)

- Dietary advice: high-fiber diet with high fluid intake
- Bulk-forming laxatives are first line - if not tolerated then lactulose should be tried
- Lubricants such as petroleum jelly may be tried before defecation
- Topical anesthetics
- Sits baths: hip baths in hot water for 2–5 minutes followed by cold water for 1 minute
- Topical steroids do not provide significant relief

Management of a **chronic** anal fissure (> 6 weeks)

- The above techniques should be continued
- Topical glyceryl trinitrate (GTN) is first line treatment for a chronic anal fissure
- If topical GTN is not effective after 8 weeks then secondary referral should be considered for surgery or botulinum toxin

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Mesenteric ischemia is primarily caused by arterial embolism resulting in infarction of the colon. It is more likely to occur in areas such as the splenic flexure that are located at the borders of the territory supplied by the superior and inferior mesenteric arteries.

Predisposing factors

- Increasing age
- Atrial fibrillation
- Other causes of emboli: endocarditis
- Cardiovascular disease risk factors: smoking, hypertension, diabetes

Features

- Abdominal pain
- Rectal bleeding
- Diarrhea
- Fever
- Bloods typically show an elevated WBC associated with acidosis (low HCO_3)

Meckel's Diverticulum:

- Presents with intermittent melena and anemia
- Diagnosed with Meckel's Scan [Technetium-99m (^{99m}Tc)] or Video Capsule Endoscopy

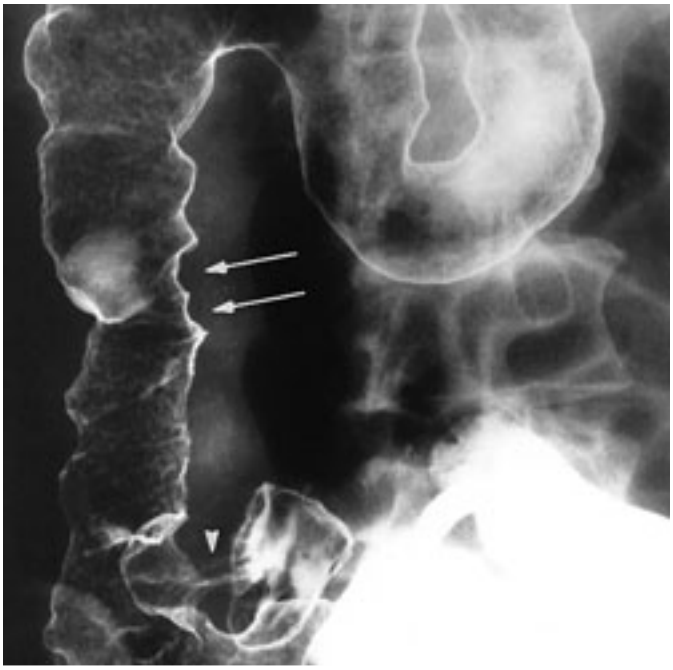
Management

- Mesenteric angiography is the diagnostic tool
- Supportive care
- Laparotomy and bowel resection

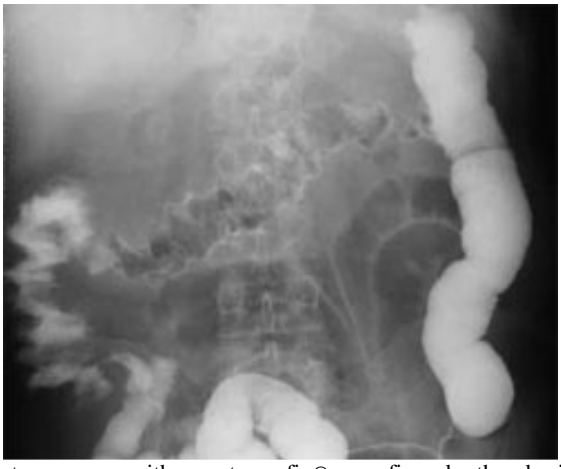
Ischemic Colitis: Although uncommon in the general population, ischemic colitis occurs with greater frequency in the elderly, and is the most common form of bowel ischemia. Causes of the reduced blood flow can include ↓BP or local factors such as constriction of blood vessels or atheroma in the mesenteric vessels (most common).

Diagnosis:

- Barium enema results tend to be abnormal in 90% showing thumbprinting, an indicative of mucosal edema
- CT is the single best test after plain radiography
- Colonoscopy is the diagnostic tool of choice: it shows petechiae, pallor, hyperemia and necrosis



Barium enema examination shows disappearance of semilunar folds, thumbprinting (arrows), narrowing of the terminal ileum (arrowhead), swelling of the ileocecal valve, and calcifications

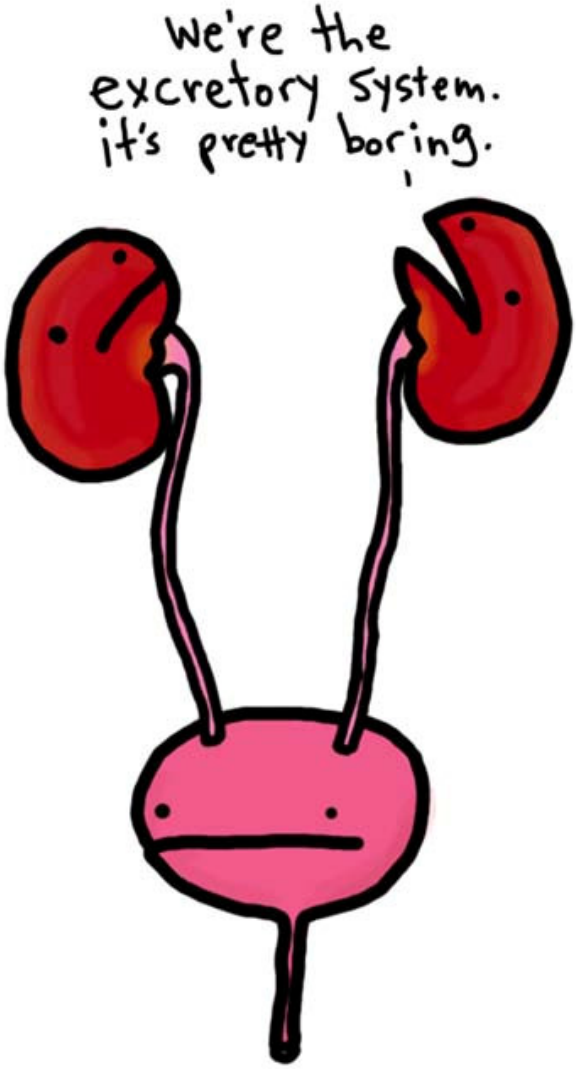


contrast enema with gastrografin® confirmed thumbprinting extending from the caecum to the splenic angle and excluded an obstructive lesion in the distal colon

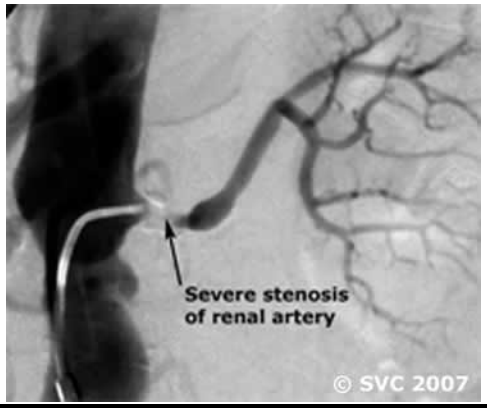
Retropritoneal Fibrosis: Lower back pain is the most common presenting feature

Associations

- Riedel's thyroiditis
- Previous radiotherapy
- Sarcoidosis
- Inflammatory abdominal aortic aneurysm
- Drugs: methysergide


We're the
excretory system.
it's pretty boring.

NEPHROLOGY



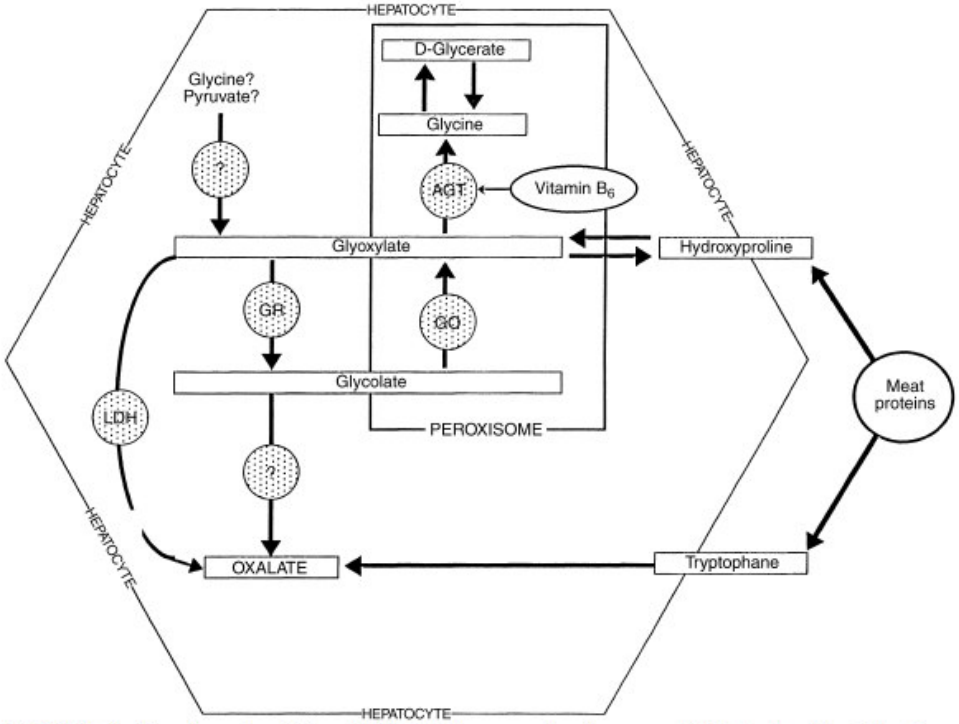


Fig. 6. Metabolic pathways from meat proteins to oxalate. Shaded circles correspond to various enzymes: AGT, alanine-glyoxylate aminotransferase; GR, glyoxylate reductase; GO, glycolate oxidase; LDH, lactate dehydrogenase. AGT deficiency causes type 1 primary hyperoxaluria, where glyoxylate cannot be metabolized to glycine, leading both glycolate and oxalate to accumulate. Vitamin B_6 supplementation may partially or completely correct the metabolic disorder.

Adrenal cortex mnemonic: GFR - ACD

Renin-Angiotensin-Aldosterone System

Adrenal cortex (mnemonic **GFR - ACD**)

- Zona **G**lomerulosa (on outside): mineralocorticoids, mainly **A**ldosterone
- Zona **F**asciculata (middle): glucocorticoids, mainly **C**ortisol
- Zona **R**eticularis (on inside): androgens, mainly **D**ehydroepiandrosterone (DHEA)

Renin

- Released by JGA cells in kidney in response to ↓ renal perfusion, low sodium
- Hydrolyses angiotensinogen to form angiotensin I

Factors stimulating renin secretion

- ↓ BP → ↓ renal prefusion
- Hyponatremia
- Sympathetic nerve stimulation
- Catecholamines
- Erect posture

Factors reducing renin secretion

- β-blockers
- NSAIDS

Angiotensin

- ACE in lung converts angiotensin I → angiotensin II
- Vasoconstriction leads to raised BP
- Stimulates thirst
- Stimulates aldosterone and ADH release

Aldosterone

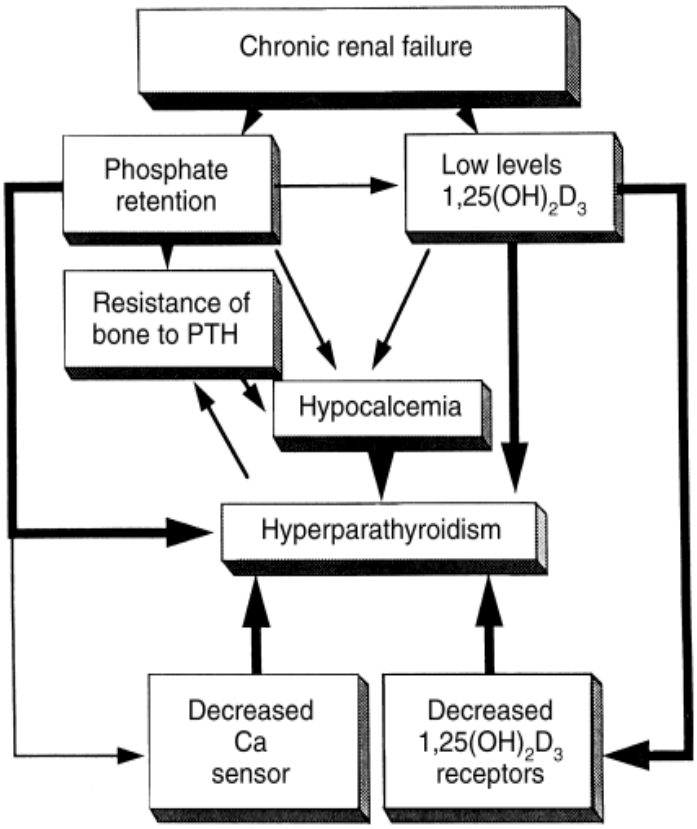
- Released by the zona glomerulosa in response to raised angiotensin II, potassium, and ACTH levels
- Causes retention of Na^+ in exchange for K^+/H^+ in distal tubule

Urine Analysis:

Normal	• Few RBCs (of normal morphology) • Fine grandular cast or hyaline cast
Glomerular Disease	➢ Dysmorphic RBCs
UTI and Pylonephritis	❖ WBCs + white cell cast
Glomerulonephritis	• Red cell casts

Basic problems in chronic kidney disease

- Low vitamin D (1-α hydroxylation normally occurs in the kidneys)
- High phosphate due to ↓ execretion.
- Low calcium: due to lack of vitamin D, high phosphate
- Secondary hyperparathyroidism: due to low calcium, high phosphate and low vitamin D



Several clinical manifestations may result:

- Osteitis fibrosa cystica
  - AKA hyperparathyroid bone disease
- Adynamic
  - Reduction in cellular activity (both osteoblasts and osteoclasts) in bone
  - May be due to over treatment with vitamin D
- Osteomalacia
  - Due to low vitamin D
- Osteosclerosis
- Osteoporosis

Anemia in CRF:

Management:

- Correction o iron with IV if needed
- Ferritin should be > 200 ng/mL before starting EPO
- EPO is used to target Hb 10-12 (>11 or hematocrit >33%) reach the target within 4 months
- Corrected Hb of > 13.5 is associate with HTN crisis
- Hb < 10.5 ↑ risk of seizures.

Erythropoietin: (EPO) is a hematopoietic growth factor that stimulates the production of erythrocytes. The main uses of erythropoietin are to treat the anemia associated with chronic renal failure and that associated with cytotoxic therapy

Side-effects of erythropoietin

- HTN and HTN crisis, potentially → encephalopathy and seizures (BP ↑ in 25% of patients)
- EPO induced seizures occurs after 90 days fro starting the treatment
- Bone aches
- Flu-like symptoms
- Skin rashes, urticaria
- Pure red cell aplasia* (due to antibodies against erythropoietin)
- Raised packed cell volume (PCV) =HCT → ↑ risk of thrombosis (e.g. Fistula)
- Iron deficiency 2nd to ↑ erythropoiesis

There are a number of reasons why patients may **fail to respond** to erythropoietin therapy

- Iron deficiency
- Inadequate dose
- Concurrent infection/inflammation
- Hyperparathyroid bone disease
- Aluminum toxicity

EPO can be detected in urine for few weeks after the latest dose

*the risk is greatly ↓ with darbepoetin

Indication for Urgent Dialysis:

- Severe acidosis
- Pulmonary edema due to volume overload
- Hyperkalemia
- Uremic pericarditis
- Severe uremic symptoms:
    - Encephalopathy
    - Vomiting

Hyperacute graft rejection is due to pre-existent antibodies to HLA antigens and is therefore IgG mediated

Renal Transplant: Graft Failure:

Graft survival

- 1 year = 90%, 10 years = 60% for cadaveric transplants
- 1 year = 95%, 10 years = 70% for living-donor transplants

Post-op problems (can cause graft dysfunction) – up to 4 months post-op:

- Acute rejection: risk is great in 1st 2 weeks occurs in 30-50% of cases
- Ciclosporin toxicity
- ATN of graft
- Vascular thrombosis
- Urine leakage
- UTI

Hyperacute graft rejection

- Due to antibodies against donor HLA type 1 antigens
- Rarely seen due to HLA matching

Management of acute graft failure (< 6 months)

- Acute rejection: give steroids, if resistant use monoclonal antibodies

Causes of chronic graft failure (> 6 months)

- Chronic allograft nephropathy
- Ureteric obstruction
- Recurrence of original renal disease (MCGN > IgA > FSGS)

Autosomal Dominant Polycystic Kidney Disease:

(ADPKD) is the most common inherited cause of kidney disease, affecting 1 in 1,000 Caucasians. Two disease loci have been identified, PKD1 and PKD2, which code for polycystin-1 and polycystin-2 respectively

ADPKD type 1	ADPKD type 2
85% of cases	15% of cases
Chromosome 16	Chromosome 4
Presents with renal failure earlier	

The screening investigation for relatives is abdominal ultrasound

Ultrasound diagnostic criteria (in patients with positive family history):

- In < 20 yrs age, CT scan is not needed
- In < 20 yrs age, ultrasound gives false –ve

} Screening is recommended after 20 yrs age

- 2 cysts, unilateral or bilateral, if aged < 30 years
- 2 cysts in both kidneys if aged 30-59 years
- 4 cysts in both kidneys if aged > 60 years

Associtaed conditions:
- Colonic diverticula (with any related symptoms, screen by barium enema)
- Mitral Valve Prolapse (needs echo screening)

Management:
- Painkillers
- Urinary tract infections: → ABX
- ↑BP control
- End-stage renal disease → Transplantation

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

is much less common than autosomal dominant disease (ADPKD). It is due to a defect in a gene located on chromosome 6

Diagnosis may be made on prenatal ultrasound or in early infancy with abdominal masses and renal failure. End-stage renal failure develops in childhood. Patients also typically have liver involvement, for example portal and interlobular fibrosis

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Nephrotic Syndrome:

Triad of
1. Proteinuria (> 3g/24hr) causing
2. Hypoalbuminemia (< 30g/L) and
3. Edema

Loss of antithrombin-III (↑↑↑), proteins C and S and associated rise in fibrinogen levels predispose to thrombosis. Loss of TBG lowers total, but not free thyroxin levels

Causes
1. Glomerulonephritis (GN, c. 80%)
   - Minimal change GN (causes 75% in children, 25% in adults)
   - Membranous GN
   - Focal Segmental GlomeruloSclerosis

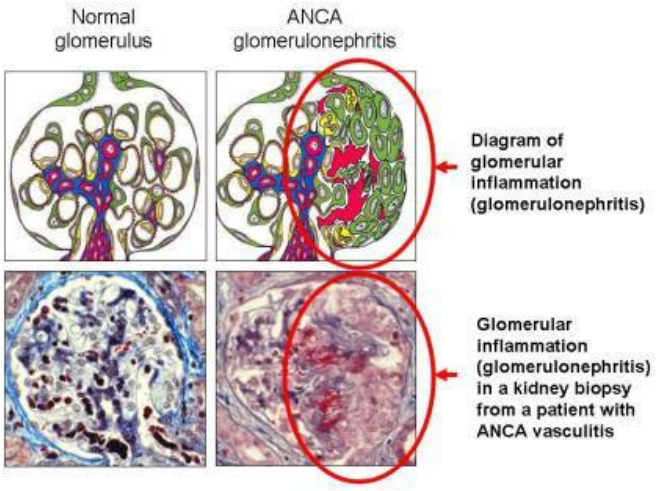
2. Systemic disease (c. 20%)
   - Amyloidosis
   - SLE

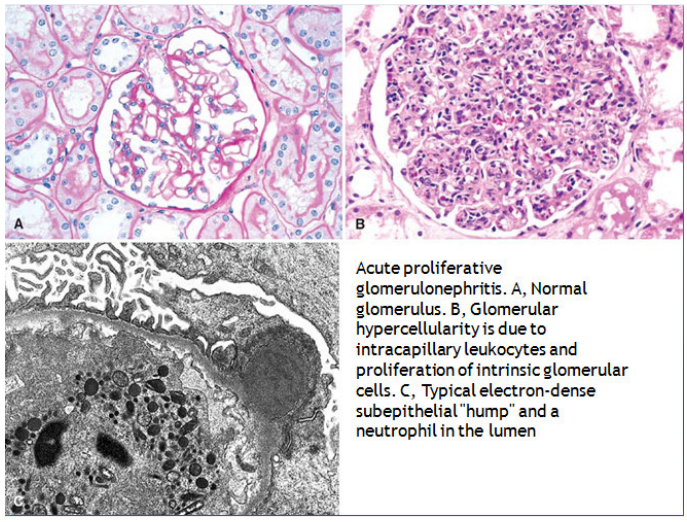
3. Drugs
   - Gold (sodium aurothiomalate), penicillamine

4. Others
   - Congenital
   - Neoplasia: carcinoma, lymphoma, leukemia, myeloma
   - Infection: bacterial endocarditis, hepatitis B, malaria
   - Renal vein thrombosis

Complications

- ↑ risk of infection due to urinary immunoglobulin loss
- ↑ risk of thromboembolism related to loss of antithrombin III and plasminogen in the urine
- Hyperlipidemia
- Hypocalcemia (vitamin D and binding protein lost in urine)
- Acute renal failure could be due to thrombotic renal veins it comes with lion pain and hematuria.





Glomerulonephritis:

1. Membranous glomerulonephritis
   - Presentation: proteinuria / nephrotic syndrome / CRF
   - Cause: infections, rheumatoid drugs, malignancy
   - 1/3 resolve, 1/3 respond to cytotoxics, 1/3 develop CRF

2. IgA nephropathy - AKA Berger's disease, mesangioproliferative GN
   - Typically young adult with **hematuria** following an URTI
   - Associated with Henoch-Schonlein purpura
   - Mesangial hypercellularity (mesangioproliferative)

3. Diffuse proliferative glomerulonephritis
   - Classical post-streptococcal glomerulonephritis in child
   - Presents as nephritic syndrome / ARF
   - Most common form of renal disease in SLE (IV)

4. Minimal change disease
   - Typically a child with nephrotic syndrome (accounts for 80%)
   - Causes: Hodgkin's, NSAIDs
   - Good response to steroids

5. Focal segmental glomerulosclerosis
   - May be idiopathic or secondary to HIV, heroin
   - Presentation: proteinuria / nephrotic syndrome / CRF

6. Rapidly progressive glomerulonephritis (RPGN) - AKA Crescentic Glomerulonephritis
   - Rapid onset, often presenting as ARF
   - Causes include Goodpasture's, ANCA positive vasculitis (e.g. Wegener's granulomatosis)

7. Mesangiocapillary glomerulonephritis (membranoproliferative)
   - Type 1: cryoglobulinemia, hepatitis C → **associated with low C4**
   - Type 2: partial lipodystrophy → **associated with low C3**

Disorders associated with glomerulonephritis and low serum C3 levels:
- Post-streptococcal glomerulonephritis
- Subacute bacterial endocarditis
- Systemic lupus erythematosus
- Mesangiocapillary glomerulonephritis

Membranous glomerulonephritis is **the commonest type of glomerulonephritis in adults** and is the third most common cause of end-stage renal failure (ESRF). It usually presents as nephrotic syndrome or proteinuria

Renal biopsy demonstrates:
- Sub-epithelial immune complex (**mainly IgG and C3**) deposition in the glomerulus
- Electron microscopy: the basement membrane is thickened with sub-epithelial electron dense deposits (IgG, C3)

Causes

- Idiopathic
- Infections: hepatitis B, malaria
- Malignancy: lung cancer, lymphoma, leukemia
- Drugs: gold, penicillamine, NSAIDs
- SLE (class V disease)

Prognosis - rule of thirds

- One-third: spontaneous remission
- One-third: remain proteinuric
- One-third: develop ESRF

Management

- Immunosuppressant: steroids, cyclophosphamide, chlorambucil e.g. Ponticelli regime
- BP control
- Consider anticoagulation

IgA Nephropathy:

Basics

- Also called Berger's disease or mesangioproliferative glomerulonephritis
- **Commonest cause of glomerulonephritis worldwide**
- Pathogenesis unknown, ?Mesangial deposition of IgA immune complexes
- Histology: mesangial hypercellularity, positive immunofluorescence for IgA & C3

Differentiating between IgA nephropathy and post-streptococcal (diffuse proliferative) glomerulonephritis:

- Post-streptococcal glomerulonephritis is associated with low complement levels
- Main symptom in post-streptococcal glomerulonephritis is proteinuria (although hematuria can occur)
- There is typically an interval between URTI and the onset of renal problems in post-streptococcal glomerulonephritis

Presentations

- Young ♂, recurrent episodes of **Hematuria, usually painless (sometimes with no renal impairment)**
- Typically associated with mucosal infections e.g., URTI
- **Nephrotic range proteinuria is rare**
- Renal failure

Associated conditions

- Alcoholic cirrhosis
- **Celiac disease**/dermatitis herpetiformis

Management

- Steroids/immunosuppressants have not shown to be useful

Prognosis

- 25% of patients develop ESRF
- Markers of good prognosis: frank hematuria
- Markers of poor prognosis: ♂ gender, proteinuria (especially > 2 g/day), hypertension, smoking, hyperlipidemia, ACE genotype DD

Minimal Change Glomerulonephritis nearly always presents as nephrotic syndrome, accounting for 75% of cases in children and 25% in adults

Minimal change glomerulonephritis - prednisolone

ACE inhibitors may be used to ↓ proteinuria in patients with heavy proteinuria or who have a slow response to prednisolone

Causes: majority of cases are idiopathic, but in around 10-20% a cause is found:

- Drugs: NSAIDs, rifampicin
- Hodgkin's lymphoma, NHL and thymoma
- Infectious mononucleosis

Features

- Nephrotic syndrome
- Normotension - hypertension is rare
- Hematuria is very rare
- Highly selective proteinuria*
- **Renal biopsy: electron microscopy shows fusion of podocytes**

Podocyte fusion is seen in minimal change glomerulonephritis but may occasionally be a feature of focal segmental glomerulosclerosis as well. Minimal change however is far more common

Management

- Majority of cases (80%) are steroid responsive
- Cyclophosphamide is the next step for steroid resistant cases

Prognosis is overall good, although relapse is common. Roughly:

- 1/3 have just one episode
- 2/3 have relapses:
    - 1/3 have infrequent relapses
    - 1/3 have frequent relapses which stop before adulthood

*only intermediate-sized proteins such as albumin and transferrin leak through the glomerulus

Mesangiocapillary Glomerulonephritis:

Overview

- AKA membranoproliferative glomerulonephritis
- May present as nephrotic syndrome, hematuria or proteinuria
- Poor prognosis

Type 1:	**Type 2** - 'dense deposit disease':
• Subendothelial immune deposits • Cause: Cryoglobulinemia (**with low C4**), hepatitis C	• Intramembranous deposits of electron dense material • Causes: **partial lipodystrophy**, factor H deficiency • ↓ serum complement • **C3**b nephritic factor (an antibody against C3bbb) found in 70% (**low C3**)

Type 3

- Causes: hepatitis B and C

Management

- Steroids may be effective

Focal Segmental Glomerulosclerosis

Causes

- Idiopathic
- Secondary to other renal pathology e.g. IgA nephropathy, reflux nephropathy
- HIV
- Heroin
- Alport's syndrome
- Sickle-cell

Presentations

- Nephrotic syndrome

Focal segmental glomerulosclerosis is noted for having a high recurrence rate in renal transplants

---

Alport's Syndrome is usually inherited in an **X-linked dominant** pattern*. It is due to a defect in the gene which codes for type IV collagen resulting in an abnormal glomerular-basement membrane (GBM). The disease is more severe in ♂s with ♀s rarely developing renal failure

A favorite question in the MRCP is an Alport's patient with a failing renal transplant. This may be caused by the presence of anti-GBM antibodies leading to a Goodpasture's syndrome like picture

Alport's syndrome usually presents in childhood. The following features may be seen:

- Microscopic hematuria
- Progressive renal failure
- Bilateral sensorineural deafness
- Lenticonus: protrusion of the lens surface into the anterior chamber
- Retinitis pigmentosa

*in around 85% of cases - 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing

---

Renal Stones:

Risk factors

- Dehydration
- Hypercalciuria, hyperparathyroidism, hypercalcemia
- Cystinuria **NOT CYSTINOSIS**
- High dietary oxalate
- Renal tubular acidosis
- Medullary sponge kidney, polycystic kidney disease
- Beryllium or cadmium exposure

Risk factors for urate stones

- Gout
- Ileostomy: loss of bicarbonate and fluid results in acidic urine, causing the precipitation of uric acid

Drug causes

- Drugs that promote calcium stones: loop diuretics, steroids, acetazolamide, theophylline
- Thiazides can prevent calcium stones (↑ distal tubular calcium resorption)

Type	Frequency	Radiograph appearance
Calcium oxalate	40%	Opaque
Mixed calcium oxalate/phosphate stones	25%	Opaque
Triple phosphate stones*	10%	Opaque
Calcium phosphate	10%	Opaque
Urate stones	5-10%	Radio-lucent
Cystine stones	1%	Semi-opaque, 'ground-glass' appearance
Xanthine stones	<1%	Radio-lucent

*stag-horn calculi involve the renal pelvis and extend into at least 2 calyces. They develop in alkaline urine and are composed of struvite (ammonium magnesium phosphate, triple phosphate). Ureaplasma urealyticum and **Proteus infections predispose to their formation**

Acute management of renal colic

Diclofenac 75 mg by intramuscular injection is the analgesia of choice for renal colic*. A second dose can be given after 30 minutes if necessary. (*PR diclofenac is an alternative)

Prevention of renal stones

Calcium stones

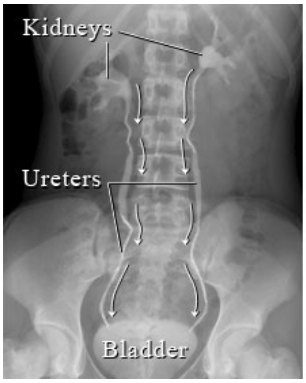
- High fluid intake
- Low animal protein, low salt diet (a low calcium diet has not been shown to be superior to a normocalcemic diet)
- Thiazide diuretics (↑ distal tubular calcium resorption)
- Stones < 5 mm will usually pass spontaneously
- Lithotripsy, nephrolithotomy may be required

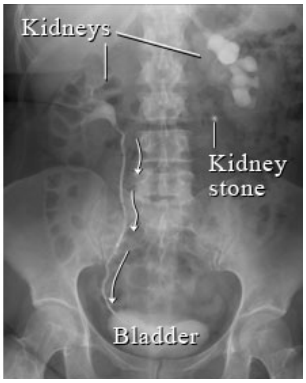
Oxalate stones

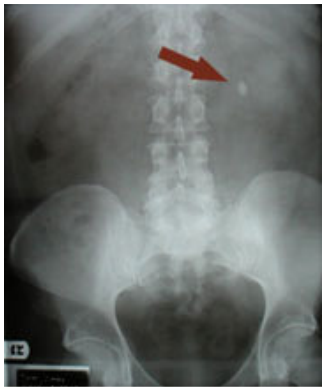
- Cholestyramine ↓ urinary oxalate secretion
- Pyridoxine ↓ urinary oxalate secretion

Uric acid stones

- Allopurinol
- Urinary alkalinization e.g. Oral bicarbonate







X-ray with contrast dye (intravenous pyelogram, or IVP) of the kidneys, ureters, and bladder. Figure 1 shows a normal flow from the kidneys, through the ureters, to the bladder (white arrows). Figure 2 shows a kidney stone blocking the normal flow of urine in the ureter.

Diabetic Nephropathy may be classified as occurring in five stages*:

Stage 1

- Hyperfiltration: ↑ in GFR (60-140 ml/min/1.73m^2)
- May be reversible

Stage 2 (silent or latent phase)

- Most patients do not develop microalbuminuria for 10 years
- GFR remains elevated

Stage 3 (incipient nephropathy)

- Microalbuminuria (albumin excretion of 30 - 300 mg/day, dipstick negative)

Stage 4 (overt nephropathy)

- Persistent proteinuria (albumin excretion > 300 mg/day, dipstick positive)
- Hypertension is present in most patients
- Histology shows diffuse glomerulosclerosis and focal glomerulosclerosis (kimmelstiel-wilson nodules)

Stage 5

- End-stage renal disease, GFR typically < 10ml/min
- Renal replacement therapy needed

The timeline given here is for type 1 diabetics. Patients with type 2 diabetes mellitus (T2DM) progress through similar stages but in a different timescale - some T2DM patients may progress quickly to the later stages

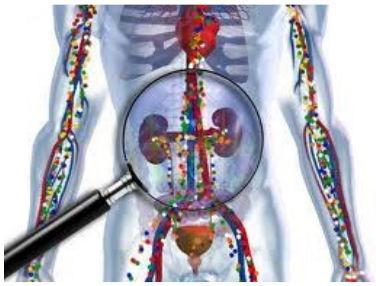
Management

Screening

- All patients should be screened annually
- Albumin:Creatinine ratio (ACR) in early morning specimen
- ACR > 2.5 = microalbuminuria

Management

- Dietary protein restriction
- Tight glycemic control
- BP control: aim for < 130/80 mmHg
- Benefits independent of blood pressure control have been demonstrated for ACE inhibitors and angiotensin II receptor blockers - these may be used alone or in combination
- Control dyslipidemia e.g. Statins



Proteinuria is an important marker of chronic kidney disease, especially for diabetic nephropathy. NICE recommend using the albumin:creatinine ratio **(ACR)** in preference to the protein:creatinine ratio (PCR) when **identifying** patients with proteinuria as it has greater sensitivity. For **quantification and monitoring** of proteinuria, **PCR** can be used as an alternative, although ACR is recommended in diabetics. Urine reagent strips are not recommended unless they express the result as an ACR.

Newly detected microalbuminuria in DM patient → repeat 3-6 months period before starting Rx

Approximate equivalent values

ACR (mg/mmol)	PCR (mg/mmol)	Urinary protein excretion (g/24 h)
30	50	0.5
70	100	1

Collecting an ACR sample

- By collecting a 'spot' sample it avoids the need to collect urine over a 24 hour period in order to detect or quantify proteinuria
- Should be a first-pass morning urine specimen
- If the initial ACR is greater than 30 mg/mmol and less than 70 mg/mmol, confirm by a subsequent early morning sample. If the initial ACR > 70 mg/mmol no need to repeat

Interpreting the ACR results

- In non-diabetics an ACR > 30 mg/mmol is considered clinically significant proteinuria
- In diabetics (ACR > 2.5 in men and ACR > 3.5 in women) is considered clinically significant

Management:

- ACE-I
- ARBs

Modification of Diet in Renal Disease (MDRD): serum creatinine may not provide an accurate estimate of renal function due to differences in muscle. For this reason formulas were developed to help estimate the glomerular filtration rate (estimated GFR or eGFR). The most commonly used formula is the (MDRD) equation, which uses the following variables:

- **Serum creatinine**
- **Age**
- **Gender**
- **Ethnicity**

CKD may be classified according to GFR:

stage	GFR range
1	> 90 ml/min, with some sign of kidney damage on other tests (if all the kidney tests* are normal, there is no CKD)
2	60-90 ml/min with some sign of kidney damage (if kidney tests* are normal, there is no CKD)
3a	45-59 ml/min, a moderate reduction in kidney function
3b	30-44 ml/min, a moderate reduction in kidney function
4	15-29 ml/min, a severe reduction in kidney function
5	Less than 15 ml/min, established kidney failure - dialysis or a kidney transplant may be needed

*i.e. normal U&Es and no proteinuria

Hematuria: the management of patients with hematuria is often difficult due to the absence of widely followed guidelines. It is sometimes unclear whether patients are best managed in primary care, by urologists or by nephrologists.

The terminology surrounding hematuria is changing. Microscopic or dipstick positive hematuria is increasingly termed non-visible hematuria whilst macroscopic hematuria is termed visible hematuria.
Causes of transient or spurious non-visible hematuria

- Urinary tract infection
- Menstruation
- Vigorous exercise
- Sexual intercourse

Causes of persistent non-visible hematuria

- Cancer (bladder, renal, prostate)
- Stones
- Benign prostatic hyperplasia, Prostatitis.
- Urethritis e.g. *Chlamydia*
- Renal causes: IgA nephropathy, thin basement membrane disease

Management
Current evidence does not support screening for hematuria. The incidence of non-visible hematuria is similar in patients taking aspirin/warfarin to the general population hence these patients should also be investigated.

Testing

- Urine dipstick is the test of choice for detecting hematuria
- Urine microscopy may be used but time to analysis significantly affects the number of red blood cells detected

NICE urgent cancer referral guidelines

- Of any age with painless macroscopic hematuria
- Aged 40 years and older who present with recurrent or persistent urinary tract infection associated with hematuria
- Aged 50 years and older who are found to have unexplained microscopic hematuria

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Fanconi syndrome describes a generalized disorder of renal tubular transport resulting in:

- Type 2 (proximal) renal tubular acidosis
- Aminoaciduria
- Glycosuria
- Phosphaturia
- Osteomalacia

Causes

- Cystinosis (most common cause in children)
- Sjogren's syndrome
- Multiple myeloma
- Nephrotic syndrome
- Wilson's disease

Renal Tubular Acidosis (RTA) all types of renal tubular acidosis (RTA) are associated with hyperchloremic metabolic acidosis (normal anion gap)

Type 1 RTA (distal)	Type 2 RTA (proximal)
• Inability to generate acid urine (secrete H+) in distal tubule • **Hypokalemia** • Complications include nephrocalcinosis and renal stones • Causes include idiopathic, RA, SLE, Sjogren's	• ↓ HCO_3- reabsorption in proximal tubule • **Hypokalemia** • Complications include osteomalacia • Causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines • Treat: Bicarb replacement + Thiazide diuretics

Type 4 RTA (**hyperkalemic** RTA) is not actually a tubular disorder at all nor does it have a clinical picture similar to the other RTAs. It was included in the classification of RTA as it is associated with a mild (normal anion gap) metabolic acidosis due to a physiological ↓ in proximal tubular ammonium excretion.

Causes include:

- Aldosterone deficiency (hypoaldosteronism): Primary vs. hyporeninemic
- Aldosterone resistance:
  - Drugs: Amiloride, Spironolactone, Trimethoprim, Pentamidine
  - Pseudohypoaldosteronism
- DM

Type	Type 1	Type 2	Type 4
Location	Distal tubules	Proximal tubules	Adrenal
Acidosis?	Yes (severe)	Yes	Mild when present
Potassium	Hypokalemia	Hypokalemia	Hyperkalemia
Pathophys	H+ secretion	Bicarb reabsorption	hypoaldosteronism/pseudohypoaldosteronism

Type 3 RTA (Juvenile RTA) is combined proximal & distal RTA.

Features:

- Results from inherited carbonic anhydrase II deficiency.
- Mutations in the gene encoding this enzyme give rise to:
  - Autosomal recessive syndrome of osteopetrosis
  - Renal tubular acidosis
  - Cerebral calcification
  - Mental retardation.
- 70% of the reported cases are from the Magreb region of North Africa

Type 3 is rarely discussed

ARF: Acute Tubular Necrosis vs Prerenal Uremia:

Prerenal uremia - kidneys hold on to sodium to preserve volume

	Pre-renal uremia	Acute tubular necrosis
Urine sodium	< 20 mmol/L	> 30 mmol/L
Fractional sodium excretion*	< 1%	> 1%
Fractional urea excretion**	< 35%	>35%
Urine:plasma osmolality	> 1.5	< 1.1
Urine:plasma urea	> 10:1	< 8:1
Specific gravity	> 1020	< 1010
Urine	'bland' sediment	Brown granular casts
Response to fluid challenge	Yes	No

*fractional sodium excretion= (urine sodium/plasma sodium)/ (urine creatinine/plasma creatinine) x100
**fractional urea excretion= (urine urea /blood urea)/ (urine creatinine/plasma creatinine) x 100

Papillary Necrosis:

Causes

- Chronic analgesia use
- Sickle cell disease
- TB
- Acute pyelonephritis
- Diabetes Mellitus

Features

- Fever, loin pain, hematuria
- IVU (intravenous urogram or IVP for pyelogram) - papillary necrosis with renal scarring - 'cup & spill'

Sterile Pyuria:

Causes

- Partially treated UTI
- Urethritis e.g. *Chlamydia, TB* and *ureaplasma urealyticum*
- Renal tuberculosis
- Renal stones
- Appendicitis
- Bladder/renal cell cancer
- Adult polycystic kidney disease
- Analgesic nephropathy

Tubulo-interstitial nephritis may cause sterile pyuria but it is not seen with acute glomerulonephritis

Renal Cell Cancer is also known as hypernephroma and accounts for 85% of primary renal neoplasms. It arises from **proximal renal tubular epithelium**

Associations*

- More common in middle-aged men
- Smoking
- Von hippel-lindau syndrome
- Tuberous sclerosis

Diagnosis:

- CT scan ± contrast shows contrast enhancing mass

Features

- Classical triad: hematuria, loin pain, abdominal mass
- Pyrexia of unknown origin
- Left varicocele (due to occlusion of left testicular vein)
- Endocrine effects: may secrete erythropoietin (polycythemia), parathyroid hormone (hypercalcemia), renin, ACTH
- 25% have metastases at presentation

Management

- Radical nephrectomy for confined disease
- α-interferon and interleukin-2 have been used to ↓ tumor size and also treat patients with metastases
- Receptor tyrosine kinase inhibitors (e.g. Sorafenib, sunitinib) have been shown to have superior efficacy compared to interferon-α

*incidence of renal cell cancer is only slightly ↑ in patients with autosomal dominant polycystic kidney disease

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Wilm's Tumor (Nephroblastoma) is one of the most common childhood malignancies. It typically presents in children less than 5 years of age, with a median age of 3 years.

most common metastatic/secondary tumor that produce a solitary round shadow in chest cavity is renal in origin

Features

- Abdominal mass (most common presenting feature)
- Painless hematuria
- Flank pain
- Other features: anorexia, fever
- Unilateral in 95% of cases
- Metastases are found in 20% of patients (most commonly lung)

Associations

- Beckwith-Wiedemann syndrome is a inherited condition associated with organomegaly, macroglossia, abdominal wall defects, Wilm's tumor and neonatal hypoglycemia
- As part of WAGR syndrome: **W**ilms **A**niridia, **G**enitourinary malformations, mental **R**etardation. It results from a deletion on chromosome 11 resulting in the loss of several genes.
- Hemihypertrophy
- Around one-third of cases are associated with a mutation in the WT1 gene on chromosome 11

Management

- Nephrectomy
- Chemotherapy
- Radiotherapy if advanced disease
- Prognosis: good, 80% cure rate

Renal Vascular Disease is most commonly due to atherosclerosis (> 95% of patients). It is associated with risk factors such as smoking and hypertension that cause atheroma elsewhere in the body. It may present as hypertension, chronic renal failure or 'flash' pulmonary edema. In younger patients however fibromuscular dysplasia (FMD) needs to be considered. **FMD** is more common in **young women** and characteristically has a 'string of beads' appearance on angiography. Patients respond well to balloon angioplasty. Its response to balloon angioplasty is better than atherosclerosis. Hypokalemia and metabolic alkalosis may occur due to compensatory hyperaldosteronism.

Investigation

- MR angiography is now the investigation of choice
- CT angiography
- Conventional renal angiography is less commonly performed used nowadays, but may still have a role when planning surgery

Flash pulmonary edema, U&Es worse on ACE inhibitor, asymmetrical kidneys
↓
Renal Artery Stenosis
↓
do MR angiography

Renal involvement in HIV patients may occur as a consequence of treatment or the virus itself. Protease inhibitors such as indinavir can precipitate intratubular crystal obstruction

HIV-associated nephropathy (HIVAN) accounts for up to 10% of end-stage renal failure cases in the United States. Antiretroviral therapy has been shown to alter the course of the disease. There are five key features of HIVAN:

- Massive proteinuria
- Normal or large kidneys
- Focal segmental glomerulosclerosis with focal or global capillary collapse on renal biopsy
- Elevated urea and creatinine
- **Normotension**

Renal Complications of SLE: WHO classification

- Class I: normal kidney
- Class II: mesangial glomerulonephritis
- Class III: focal (and segmental) proliferative glomerulonephritis
- Class IV: diffuse proliferative glomerulonephritis
- Class V: diffuse membranous glomerulonephritis
- Class VI: sclerosing glomerulonephritis

Class IV (diffuse proliferative glomerulonephritis) is the most common and severe form of proliferative GN

Management

- Treat hypertension
- Corticosteroids if clinical evidence of disease
- Immunosuppressants e.g. Azathioprine/cyclophosphamide

CKD & HTN: The majority of patients with chronic kidney disease (CKD) will require more than two drugs to treat hypertension. ACE inhibitors are first line and are particularly helpful in proteinuric renal disease (e.g. diabetic nephropathy). As these drugs tend to ↓ filtration pressure a small fall in glomerular filtration pressure (GFR) and rise in creatinine can be expected. Most nephrologists would accept a change of up to 15%. A rise greater than this may indicate underlying renovascular disease.

Furosemide is useful as anti-hypertensive in patients with CKD, particularly when the GFR falls to below 45 ml/min*. It has the added benefit of lowering serum potassium. High doses are usually required. If the patient becomes at risk of dehydration (e.g. Gastroenteritis) then consideration should be given to temporarily stopping the drug

*the NKF K/DOQI guidelines suggest a lower cut-off of less than 30 ml/min

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Goodpasture's syndrome (AKA anti-glomerular basement membrane disease) is a rare condition characterized by glomerulonephritis and hemorrhaging of the lungs. Although many diseases can present with these symptoms, the name Goodpasture's syndrome is usually reserved for the autoimmune disease triggered when the patient's immune system attacks Goodpasture antigen (a type II hypersensitivity reaction), which is found in the kidney and lung, and in time, causing damage to these organs.

Goodpasture's syndrome
- Ig**G** deposits on renal biopsy
- Anti-**G**BM antibodies

Goodpasture's syndrome is rare condition associated with both pulmonary hemorrhage and rapidly progressive glomerulonephritis. It is caused by anti-glomerular basement membrane (anti-GBM) antibodies against type IV collagen. Goodpasture's syndrome is more common in men (sex ratio 2:1) and has a bimodal age distribution (peaks in 20-30 and 60-70 age bracket). Associated with HLA DR2.

Features

- Pulmonary hemorrhage
- Followed by rapidly progressive glomerulonephritis

Factors which ↑ likelihood of pulmonary hemorrhage

- Young ♂s
- Smoking
- Lower respiratory tract infection
- Pulmonary edema
- Inhalation of hydrocarbons

Investigations

- Renal biopsy: linear IgG deposits along basement membrane
- ↑ transfer factor secondary to pulmonary hemorrhages
- Lung biopsy: accumulation of hemosidren laden macrophages with alveoli

Management

- Plasma exchange
- Steroids
- Cyclophosphamide

Dehydration may ↓ the likelihood of a pulmonary hemorrhage. Pulmonary edema is associated with ↑ risk

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Hemolytic Uremic Syndrome is generally seen in young children and produces a triad of:

- Acute renal failure
- Microangiopathic hemolytic anemia
- Thrombocytopenia

Causes

- Post-dysentery - classically E coli 0157:H7 ('verotoxigenic', 'enterohemorrhagic')
- Tumors
- Pregnancy
- Cyclosporine, the Pill
- SLE
- HIV

Investigations

- Full blood count: anemia, thrombocytopenia, fragmented blood film
- U&E: acute renal failure
- Stool culture

Management

- Treatment is supportive e.g. Fluids, blood transfusion and dialysis if required
- There is no role for antibiotics, despite the preceding diarrheal illness in many patients
- The indications for **plasma exchange** in HUS are complicated. As a general rule plasma exchange is reserved for **severe cases of HUS NOT associated with diarrhea**

Phenylketonuria (PKU) is an autosomal recessive condition caused by a disorder of phenylalanine metabolism. This is due to defect in phenylalanine hydroxylase, an enzyme which converts phenylalanine to tyrosine. High levels of phenylalanine lead to problems such as learning difficulties and seizures. The gene for phenylalanine hydroxylase is located on chromosome 12. The incidence of PKU is c. 1 in 10,000 live births

Features

- Usually presents by 6 months e.g. With developmental delay
- Child classically has fair hair and blue eyes
- Learning difficulties
- Seizures, typically infantile spasms
- Eczema
- 'Musty' odor to urine and sweat*

Diagnosis

- Guthrie test: the 'heel-prick' test done at 5-9 days of life - also looks for other biochemical disorders such as hypothyroidism
- Hyperphenylalaninemia
- Phenylpyruvic acid in urine

Management

- Poor evidence base to suggest strict diet prevents learning disabilities
- Dietary restrictions are however important during pregnancy as genetically normal fetuses may be affected by high maternal phenylalanine levels

*secondary to phenylacetate, a phenylketone

Cystinuria is an autosomal recessive disorder characterized by the formation of recurrent renal stones. It is due to a defect in the membrane transport of cystine, ornithine, lysine, arginine (mnemonic = COLA)

Genetics

- Chromosome 2: SLC3A1 gene, chromosome 19: SLC7A9

Features

- Recurrent renal stones
- Are classically yellow and crystalline, appearing semi-opaque on x-ray

Diagnosis

- Cyanide-nitroprusside test

Management

- Hydration
- D-penicillamine
- Urinary alkalinization

Homocystinuria is a rare autosomal recessive disease caused by deficiency of cystathione β-synthetase. This results in an accumulation of homocysteine which is then oxidized to homocysteine.

Features

- Often patients have fine, fair hair
- Musculoskeletal: may be **similar to Marfan's** - arachnodactyly etc
- **Neurological** patients may have learning difficulties, seizures
- **Ocular: downwards dislocation of lens (Marfan has upward dislocation of lens)**
- ↑ Risk of arterial and venous thromboembolism except coronaries.
- Also malar flush, livedo reticularis

Diagnosis is made by the cyanide-nitroprusside test, which is also positive in cystinuria

Treatment is vitamin B6 supplements

Alkaptonuria: (black urine disease or alcaptonuria)

Basics:

- Rare inherited genetic disorder of phenylalanine and tyrosine metabolism
- Autosomal recessive
- Common in Slovakia and the Dominican Republic than in other countries.
- Due to a defect in the enzyme homogentisate 1,2-dioxygenase, which participates in the degradation of tyrosine. As a result, a toxic tyrosine byproduct called homogentisic acid (or alkapton) accumulates in the blood and is excreted in urine in large amounts. Excessive homogentisic acid causes damage to cartilage (ochronosis, leading to **osteoarthritis**) and **heart valves** as well as precipitating as **kidney stones**.

Alkaptonuria is often asymptomatic, but the **sclera may be pigmented** (often only at a later age), and the **skin may be darkened in sun-exposed areas** and around sweat glands; **sweat may be colored brown or black.** Kidney stones and stone formation in the prostate (in men) are common and may occur in more than a quarter of cases.

The main symptoms of alkaptonuria are due to the accumulation of homogentisic acid in tissues. In the joints this leads to cartilage damage, specifically in the spine, leading **to low back pain** at a young age in most cases. Cartilage damage may also occur in the **hip and shoulder. Joint replacement surgery** (hip and shoulder) is often necessary at a relatively young age.

Valvular heart disease, mainly calcification and regurgitation of the aortic and mitral valves, may occur, and in severe and progressive cases valve replacement may be necessary. Coronary artery disease may be accelerated in alkaptonuria.

A distinctive characteristic of alkaptonuria is that **ear wax exposed to air turns red or black** (depending on diet) after several hours because of the accumulation of homogentisic acid

Treatment with nitisinone, which suppresses homogentisic acid production, is being studied

Benign prostatic hyperplasia (BPH) is a common condition seen in older men.

Risk factors

- Age: around 50% of 50-year-old men will have evidence of BPH and 30% will have symptoms. Around 80% of 80-year-old men have evidence of BPH
- Ethnicity: Black > White > Asian

BPH typically presents with lower urinary tract symptoms (LUTS), which may be categorized into:

- Voiding symptoms (obstructive): weak or intermittent urinary flow, straining, hesitancy, terminal dribbling and incomplete emptying
- Storage symptoms (irritative) urgency, frequency, urgency incontinence and nocturia
- Post-micturition: dribbling
- Complications: urinary tract infection, retention, obstructive uropathy

Management options

- Watchful waiting
- Medication: α-1 antagonists, 5 α-reductase inhibitors. The use of combination therapy was supported by the medical therapy of prostatic symptoms (MTOPS) trial
- Surgery: transurethral resection of prostate (TURP)

α-1 antagonists e.g. tamsulosin, alfuzosin

- ↓ smooth muscle tone (prostate and bladder)
- Considered first-line, improve symptoms in around 70% of men
- Adverse effects: dizziness, postural hypotension, dry mouth, depression

5 α-reductase inhibitors e.g. finasteride

- Block the conversion of testosterone to dihydrotestosterone (DHT), which induces BPH
- Unlike α-1 antagonists causes a reduction in prostate volume and hence may slow disease progression. This however takes time and symptoms may not improve for 6 months. They may also ↓ PSA concentrations by up to 50%
- Adverse effects: erectile dysfunction, ↓ libido, ejaculation problems, gynecomastia

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Prostate cancer:

Risk Factors:

- Age
- ↑ fat diet
- Family Hx
- **BPH is not a risk factor**

Management

Localized disease = T1/2

T1 - clinically unapparent disease:

- If life expectancy < 10 years then watchful waiting
- If life expectancy > 10 years then offer:
    - Radical prostatectomy
    - Radical radiotherapy

T2 - palpable disease confined to prostate

- Radical prostatectomy
- Radical radiotherapy (often if older patient)

Locally advanced disease (T3/4)

- T3 = beyond prostatic capsule
- T4 = involves bladder neck or rectum
- Most men will have occult mets

} Radiotherapy

Disseminated disease - hormonal therapy

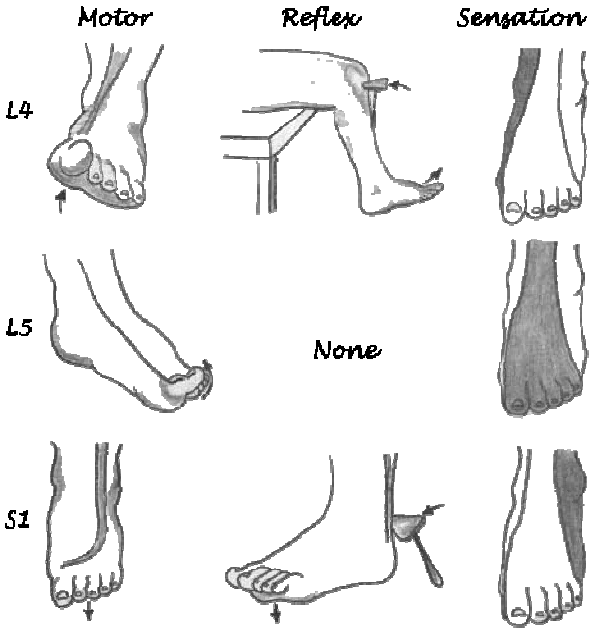
- Synthetic GnRH agonist
  - E.g. Goserelin (zoladex) is a synthetic GnRH agonist which provides negative feedback to the anterior pituitary.
  - Cover initially with anti-androgen to prevent rise in testosterone
- Anti-androgen:
  - Cyproterone acetate prevents DHT binding from intracytoplasmic protein complexes
- Orchidectomy

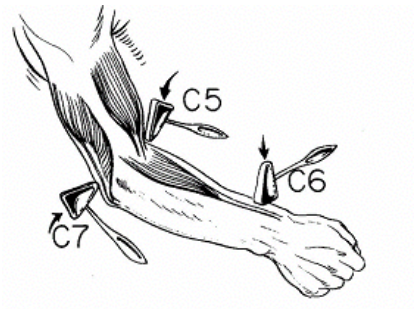
Bladder cancer: is a common urological cancer with most cases being transitional cell carcinomas. It has a ♂:♀=3:1 with women generally having a worse prognosis than men. The most classical presentation is with total, gross, painless hematuria.

Associated Factors:

- Smoking
- Occupational: aniline dyes used in printing and textile industry, rubber manufacture
- Aromatic amines
- Prior radiation treatment to the pelvis
- Exposure to a urinary metabolite of cyclophosphamide (acrolein).
- Schistosomiasis (S. hematobium infection)
- Mutations on 17p13.1, the gene coding for p53, mutations of which are associated with high-grade bladder cancer
- Mutation on 9p15 and 9p16, another tumor suppressor gene associated with low grade and superficial tumors.
- Drugs: cyclophosphamide
- ***There is NO significant correlation between bladder cancer and coffee consumption, artificial sweetener intake or aspirin ingestion.***

LOCOMOTOR





N.B.: locomotor questions usually come as part of neurology or basic science

Nerve Roots:

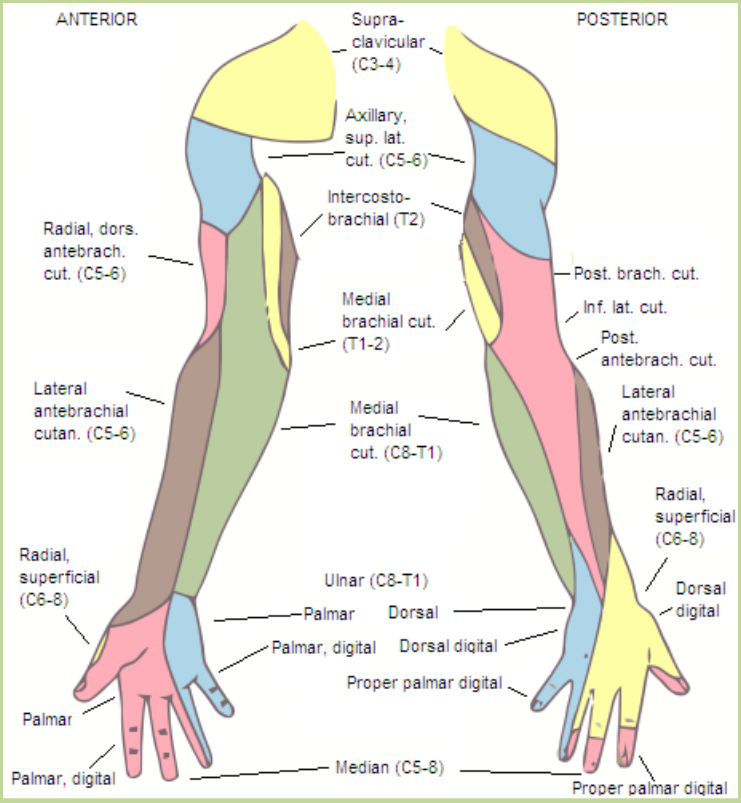
Reflex	Root
Biceps	C5-C6
Triceps	C7-C8
Knee	L3-L4
Ankle	S1-S2

Muscle	Root
Deltoid	C5
Triceps	C7
Quarreceps	L3
Long Flexor	L8
Gastrocnemius	S1

Deltoid muscle:

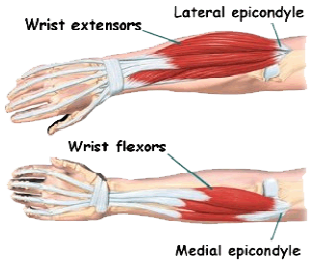
- Supplied by the axillary nerve (C5,C6)
- Actions: mainly shoulder abduction

FYI
For Your Information



Elbow Pain

The table below details some of the characteristic features of conditions causing elbow pain:



Lateral epicondylitis (tennis elbow)	Features • Pain and tenderness localized to the lateral epicondyle • Pain worse on resisted wrist extension with the elbow extended or supination of the forearm with the elbow extended also there is pain on middle finger extension • Episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks
Medial epicondylitis (golfer's elbow)	Features • Pain and tenderness localized to the medial epicondyle • Pain is aggravated by wrist flexion and pronation • Symptoms may be accompanied by numbness / tingling in the 4th and 5th finger due to ulnar nerve involvement
Radial tunnel syndrome	Most commonly due to compression of the posterior interosseous branch of the radial nerve. It is thought to be a result of overuse. Features • Symptoms are similar to lateral epicondylitis making it difficult to diagnose • However, the pain tends to be around 4-5 cm distal to the lateral epicondyle • Symptoms may be worsened by extending the elbow and pronating the forearm, not like tennis elbow where supinating is the problem
Cubital tunnel syndrome	Due to the compression of the ulnar nerve. Features • Initially intermittent tingling in the 4th and 5th finger • May be worse when the elbow is resting on a firm surface or flexed for extended periods • Later numbness in the 4th and 5th finger with associated weakness
Olecranon bursitis	Swelling over the posterior aspect of the elbow. There may be associated pain, warmth and erythema. It typically affects middle-aged male patients.

De Quervain's Tenosynovitis is a common condition in which the sheath containing the extensor pollicis brevis and abductor pollicis longus tendons is inflamed. It typically affects females aged 30 - 50 years old

Features

- Pain on the radial side of the wrist
- Tenderness over the radial styloid process
- Abduction of the thumb against resistance is painful
- Finkelstein's test: with the thumb is flexed across the palm of the hand, pain is reproduced by movement of the wrist into flexion and ulnar deviation

Management

- Analgesia
- Steroid injection
- Immobilization with a thumb splint (SPICA) may be effective
- Surgical treatment is sometimes required

Lateral Epicondylitis typically follows unaccustomed activity such as house painting or playing tennis ('tennis elbow'). It is most common in people aged 45-55 years and typically affects the dominant arm.

Features

- Pain localized to the lateral epicondyle
- Pain worse on resisted wrist extension with the elbow extended or supination of the forearm with the elbow extended
- Episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks

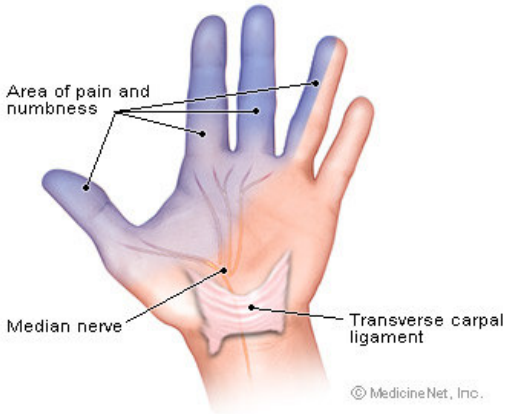
Management options

- Advice on avoiding muscle overload
- Simple analgesia
- Steroid injection
- Physiotherapy

Carpal Tunnel Syndrome is caused by compression of **MEDIAN NERVE** in the carpal tunnel

History

- Pain/pins and needles in thumb, index, middle finger e.g. At night
- Patient flicks hand to obtain relief



Examination

- Weakness of thumb abduction
- Wasting of thenar eminence (**NOT HYPOTHENAR**)
- Tinel's sign: tapping causes paraesthesia
- Phalen's sign: flexion of wrist causes symptoms

Causes: pregnancy, premenstrual, edema (CCF), lunate fracture, RA

Electrophysiology

- Motor + sensory: prolongation of the action potential

Treatment

- Carpal injection
- Wrist splints at night
- Surgical decompression (flexor retinaculum division)

Median Nerve:

Arm: The median nerve has no voluntary motor or cutaneous function in the (upper) arm. It gives vascular branches to the wall of the brachial artery. These vascular branches carry sympathetic fibers.

Forearm: It innervates all of the flexors in the forearm except flexor carpi ulnaris and that part of flexor digitorum profundus that supplies the medial two digits. The latter two muscles are supplied by the ulnar nerve (specifically the Muscular branches of ulnar nerve).
The main portion of the median nerve supplies the following muscles:

Superficial group:

- Pronator teres
- Flexor carpi radialis
- Palmaris longus

Intermediate group:

- Flexor digitorum superficialis muscle

The anterior interosseus branch of the median nerve supplies the following muscles:

Deep group:

- Flexor digitorum profundus (only the lateral half)
- Flexor pollicis longus
- Pronator quadratus

Hand: it supplies motor innervation to the 1st and 2nd lumbrical muscles. It also supplies the muscles of the thenar eminence by a recurrent thenar branch. The rest of the intrinsic muscles of the hand are supplied by the ulnar nerve.

The median nerve innervates the skin of the palmar side of the thumb, the index and middle finger, half the ring finger, and the nail bed of these fingers. The lateral part of the palm is supplied by the palmar cutaneous branch of the median nerve, which leaves the nerve proximal to the wrist creases. This palmar cutaneous branch travels in a separate fascial groove adjacent to the flexor carpi radialis and then superficial to the flexor retinaculum. It is therefore spared in carpal tunnel syndrome.

The muscles of the hand supplied by the median nerve can be remembered using the mnemonic, "LOAF" for Lumbricals 1 & 2, Opponens pollicis, Abductor pollicis brevis and Flexor pollicis brevis.

Injury: at different levels cause different syndromes.

- Injury of this nerve at a level above the elbow results in loss of pronation and a reduction in flexion of the hand at the wrist.
- Entrapment at the level of the elbow or the proximal forearm could be due to the pronator teres syndrome.
- Injury to the anterior interosseous branch in the forearm causes the anterior interosseous syndrome.
- Injury by compression at the carpal tunnel causes carpal tunnel syndrome.
- Severing the median nerve causes median claw hand.
- In the hand, thenar muscles are paralyzed and will atrophy over time. Opposition and flexion of the thumb are lost. The thumb and index finger are arrested in adduction and hyperextension. This appearance of the hand is collectively referred as 'ape hand deformity'.

Anterior Interosseous Nerve: is the largest branch of the median nerve arising distal to the lateral epicondyl. It is a favorite nerve in MRCP-I. It accounts for < 1% of all compression palsies in the upper limb.

It supplies:

- Flexor pollicis longus
- Felxer digtorium profundus to the index and sometimes middle finger
- Pronator quadrates

The typical symptoms:

- Inability to oppose the thumb and index finger
- Inability to flex the thumb IP joint
- Inability to flex the distal IP joint of the index
- Pronator quadrates paralyzed

Causes: traumatic and non traumatic etiology

Radial Nerve: arises from the posterior cord of the brachial plexus (C5-8)

Motor to

- Extensor muscles (forearm, wrist, fingers, thumb)

Sensory to

- Dorsal aspect of lateral 3 1/2 fingers
- However, only small area between the dorsal aspect of the 1st and 2nd metacarpals is exclusively by the radial nerve

Patterns of damage

- Wrist drop
- Sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals

Axillary damage

- As above
- Paralysis of triceps

Ulnar Nerve: arises from medial cord of brachial plexus (C8, T1)

Motor to	Sensory to
• Medial two lumbricals • ADductor pollicis • Interossei • Hypothenar muscles: ABductor digiti minimi, flexor digiti minimi • Flexor carpi ulnaris	• Medial 1 1/2 fingers (palmar and dorsal aspects)

Patterns of damage

Damage at wrist	Damage at elbow
• 'Claw hand' • Wasting and paralysis of intrinsic hand muscles (except lateral two lumbricals) • Wasting and paralysis of hypothenar muscles • Sensory loss to the medial 1 1/2 fingers (palmar and dorsal aspects)	• As above • Radial deviation of wrist

Adhesive Capsulitis (frozen shoulder) has a known association with diabetes. Patients typically have a painful freezing phase, an adhesive phase and a recovery phase. The episode typically lasts 2-3 years.

Diabetic Amyotrophy: **or proximal diabetic neuropathy** or **lumbosacral radiculoplexus neuropathy**, is a diabetic neuropathy characterized by painful muscle wasting and weakness. It affects the lower limbs and is typically asymmetric. Proximal diabetic neuropathy typically occurs in aged type 2 diabetic males, though it may occur in younger diabetic patients and females.

Lower Back Pain (LBP)

is one of the most common presentations seen in practice. Whilst the majority of presentations will be of a non-specific muscular nature it is worth keeping in mind possible causes which may need specific treatment.

Red flags for lower back pain

- Age < 20 years or > 50 years
- History of previous malignancy
- Night pain
- History of trauma
- Systemically unwell e.g. Weight loss, fever

The table below indicates some related problems:

Facet joint	May be acute or chronic Pain worse in the morning and on standing On examination there may be pain over the facets. The pain is typically worse on extension of the back
Spinal stenosis	Usually gradual onset Unilateral or bilateral **leg pain** (with or without back pain), numbness, and weakness which is worse on walking. **Resolves when sits down**. Pain may be described as 'aching', 'crawling'. Relieved by sitting down, leaning forwards and crouching down Clinical examination is often normal Requires MRI to confirm diagnosis
Ankylosing spondylitis	Typically a young man who presents with lower back pain and stiffness Stiffness is usually worse in morning and improves with activity Peripheral arthritis (25%, more common if ♀)
Peripheral arterial disease	**Pain on walking, relieved by rest** Absent or **weak foot pulses** and other signs of limb ischemia Past history may include smoking and other vascular diseases

Prolapsed lumbar disc usually produces clear dermatomal leg pain associated with neurological deficits.

Features

- Leg pain usually worse than back
- Pain often worse when sitting

Spinal Cord Compression

Spinal Cord Compression is an oncological emergency and affects up to 5% of cancer patients. It is more common in patients with lung, breast and prostate cancer

Features

- Back pain: may be worse on lying down and coughing
- Neurological signs depend on the level of the lesion. Tendon **reflexes tend to be increased below the level of the lesion and absent at the level of the lesion**

Management

- High-dose oral dexamethasone
- Urgent oncological assessment for consideration of radiotherapy or surgery

This table demonstrates the expected features according to the level of compression:

L3 nerve root compression	Sensory loss from anterior thigh to medial aspect of lower leg Weak quadriceps ↓ knee reflex Positive femoral stretch test
L4 nerve root compression	Sensory loss anterior aspect of knee Weak quadriceps ↓ knee reflex Positive femoral stretch test
L5 nerve root compression	Sensory loss dorsum of foot Weakness in foot and big toe dorsiflexion Reflexes intact Positive sciatic nerve stretch test
S1 nerve root compression	Sensory loss posterolateral aspect of leg and lateral aspect of foot Weakness in plantar flexion of foot ↓ ankle reflex Positive sciatic nerve stretch test

Management

- Similar to that of other musculoskeletal lower back pain: analgesia, physiotherapy, exercises
- If symptoms persist then referral for consideration of MRI is appropriate

Common Peroneal Nerve Lesion

The sciatic nerve divides into the tibial and common peroneal nerves. Injury often occurs at the neck of the fibula

The most characteristic feature of a common peroneal nerve lesion is foot drop

Other features include:

- Weakness of foot dorsiflexion
- Weakness of foot eversion
- Weakness of extensor hallucis longus
- Sensory loss over the dorsum of the foot and the lower lateral part of the leg
- Wasting of the anterior tibial and peroneal muscles

Baker Cyst (Popliteal Cyst)

- Most common mass in the popliteal fossa
- Since the cyst is an extension from the knee joint, it is lined by synovium.
- Ultrasound is the investigation of choice in the evaluation of a popliteal mass.
- Complication: most common is rupture or dissection of fluid into the adjacent proximal gastrocnemius muscle belly which results in a syndrome mimicking the symptoms of a deep vein thrombosis. Doppler ultrasound will, however, show the vascular lumen to be compressible (the lumen is not compressible in DVT due to the presence of the thrombus).

Conditions associated with popliteal cysts, in descending order of frequency, are as follows:

- Arthritides
- Osteoarthritis
- Rheumatoid arthritis
- Juvenile arthritis
- Gout
- Reiter's syndrome
- Psoriasis
- Systemic lupus erythematosus
- Internal derangement (meniscal tears, anterior cruciate ligamaent (ACL) tears, osteochondral fractures)
- Infection (septic arthritis, tuberculosis)
- Chronic dialysis
- Hemophilia
- Hypothryroidism
- Pigmented villonodular synovitis
- Sarcoidosis

Ankle Injury: the Ottawa Rules with for ankle x-rays have a sensitivity approaching 100%

Ankle x-ray is required only if there is any pain in the malleolar zone and + 1 of the following findings:

- Bony tenderness at the lateral malleolar zone (from the tip of the lateral malleolus to include the lower 6 cm of posterior border of the fibular)
- Bony tenderness at the medial malleolar zone (from the tip of the medial malleolus to the lower 6 cm of the posterior border of the tibia)
- Inability to walk four weight bearing steps immediately after the injury and in the emergency department

There are also Ottawa rules available for both foot and knee injuries

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Osteomalacia:

The low calcium and phosphate combined with the raised alkaline phosphatase point towards osteomalacia

Basics

- Normal bony tissue but ↓ mineral content
- Rickets if when growing
- Osteomalacia if after epiphysis fusion

Types

- Vitamin D deficiency e.g. Malabsorption, lack of sunlight, diet
- Renal failure
- Drug induced e.g. Anticonvulsants
- Vitamin D resistant; inherited
- Liver disease, e.g. Cirrhosis

Features

- Rickets: knock-knee, bow leg, features of hypocalcemia
- Osteomalacia: bone pain, fractures, muscle tenderness, proximal myopathy

Investigation

- Low Ca^2, PO34-, 25(OH) vitamin D
- Raised ALP
- X-ray: children - cupped, ragged metaphyseal surfaces; adults - translucent bands (**Looser's zones or pseudofractures**)

Treatment

- Calcium with vitamin D tablets

Osteoporosis: Risk factors:

- Family history
- ♀ sex
- Increasing age
- Deficient diet
- Sedentary lifestyle
- Smoking
- Premature menopause
- **low body weight**
- Asians and Orientals
- Research is ongoing, whether warfarin is a risk factor

♂ with osteoporosis without significant Hx → check testosterone

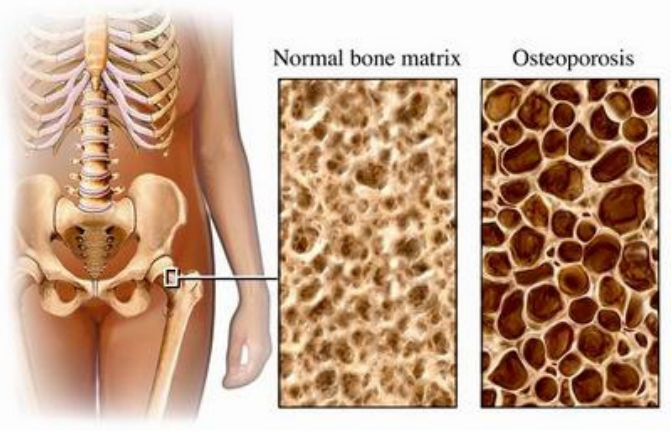
Diseases which predispose

- Endocrine: **glucocorticoid excess** (e.g. Cushing's, steroid therapy), **hyperthyroidism, hyperparathyroidism**, **hypoGonadism (e.g. Turner's), Growth hormone deficiency, diabetes mellitus (Glucose)**
- Multiple myeloma, lymphoma
- GI problems: malabsorption (e.g. Celiac), gastrectomy, liver disease
- Rheumatoid arthritis
- Long term heparin therapy*
- Chronic renal failure
- Osteogenesis imperfecta, homocystinuria

Secondary prevention

NICE guidelines were updated in 2008 on the secondary prevention of osteoporotic fractures in postmenopausal women.

Key points include



- Treatment is indicated following osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis (**a T-score of – 2.5 SD or below**). In women aged 75 years or older, a DEXA scan may not be required 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'
- Vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
- **Alendronate is first-line**
- Around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered risedronate or etidronate (see treatment criteria below)
- Strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below). Raloxifene may actually decrease the risk of breast cancer.

Treatment criteria for patients not taking alendronate

Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate

Risk factors

- Parental history of hip fracture
- Alcohol intake of 4 or more units
- Rheumatoid arthritis

<u>Supplementary notes on treatment</u>

Bisphosphonates

- Alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- All three have been shown to ↓ the risk of both vertebral and non-vertebral fractures although **alendronate, risedronate may be superior to etidronate** in preventing hip fractures
- **Ibandronate is a once-monthly oral bisphosphonate**

Vitamin D and calcium

- Poor evidence base to suggest ↓ fracture rates in the general population at risk of osteoporotic fractures - may ↓ rates in frail, housebound patients

Raloxifene - selective estrogen receptor modulator (SERM)

- Has been shown to prevent bone loss and to ↓ the risk of vertebral fractures, but has not yet been shown to ↓ the risk of non-vertebral fractures

- Has been shown to ↑ bone density in the spine and proximal femur
- **May worsen menopausal symptoms**
- **↑ risk of thromboembolic events**
- May ↓ risk of breast cancer

Strontium ranelate

- 'Dual action bone agent' - ↑ deposition of new bone by osteoblasts and ↓ the resorption of bone by osteoclasts
- Strong evidence base, may be second-line treatment in near future
- ↑ risk of thromboembolic events

Teriparatide

- Recombinant form of parathyroid hormone
- Very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined

Hormone replacement therapy

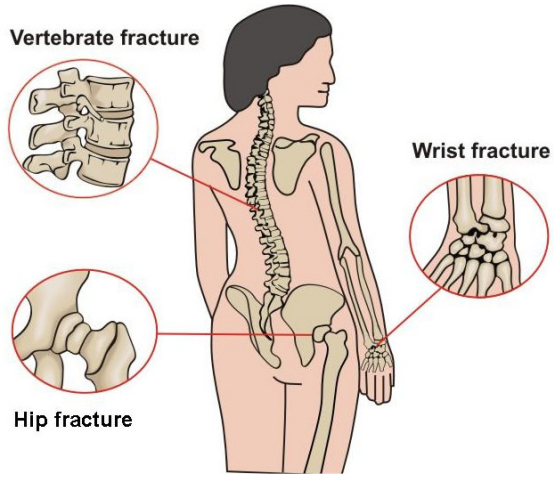
- Has been shown to ↓ the incidence of vertebral fracture and non-vertebral fractures
- **Due to concerns about ↑ rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms**

Hip protectors

- Evidence to suggest significantly ↓ hip fractures in nursing home patients
- Compliance is a problem

Falls risk assessment

- No evidence to suggest ↓ fracture rates
- However, do ↓ rate of falls and should be considered in management of high risk patients



Patients who take the equivalent of **prednisolone 7.5 mg or more each day for 3 months** or longer **should be assessed and** where necessary **given osteoporosis prophylactic treatment**

Assessment for treatment - patients taking the equivalent of prednisolone 7.5 mg or more each day for 3 months, and one of the following

- Are over the age of 65 years
- Have a history of a fragility fracture
- Have a T-score less than - 1.5 SD

Treatment

- First-line: oral bisphosphonate
- Second-line: alfacalcidol or calcitriol

Paget's Disease is a disease of ↑ but uncontrolled bone turnover. It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by ↑ osteoblastic activity. Paget's disease is common (UK prevalence 5%) and symptomatic in only 5%.

Predisposing factors

- Increasing age
- ♂ sex
- Northern latitude
- Family history

Clinical features - only 5% of patients are symptomatic

Normal calcium and phosphate combined with a raised alkaline phosphate

- Bone pain (e.g. Pelvis, lumbar spine, femur)
- Classical, untreated features: bowing of tibia, bossing of skull
- Raised alkaline phosphatase (ALP) - calcium* and phosphate are typically normal
- Skull x-ray: thickened vault, osteoporosis circumscripta

Indications for treatment include bone pain, skull or long bone deformity, fracture, periarticular Paget's

- Bisphosphonate (either oral risedronate or IV zoledronate)
- Calcitonin is less commonly used now

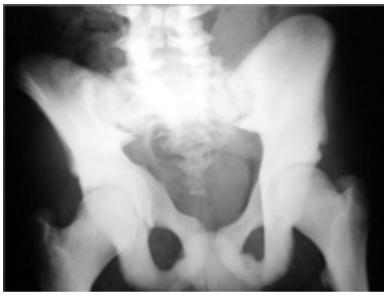
Complications

- Deafness (cranial nerve entrapment)
- Bone sarcoma (1% if affected for > 10 years)
- Fractures
- Skull thickening
- High-output cardiac failure

*usually normal in this condition but hypercalcemia may occur with prolonged immobilization

Osteopetrosis

- AKA marble bone disease
- Rare disorder of defective osteoclast function resulting in failure of normal bone resorption
- Stem cell transplant and interferon-gamma have been used for treatment



Osteogenesis Imperfecta (more commonly known as **brittle bone disease**) is a group of disorders of collagen metabolism resulting in bone fragility and fractures. The most common, and milder, form of osteogenesis imperfecta is type 1

Overview

- Autosomal dominant
- Abnormality in type 1 collagen due to ↓ synthesis of pro-α 1 or pro-α 2 collagen polypeptides

Features

- Presents in childhood
- Fractures
- Blue sclera
- Deafness secondary to otosclerosis

Rhabdomyolysis will typically feature in the exam as a patient who has had a fall or prolonged epileptic seizure and is found to have acute renal failure on admission

Features

- Acute renal failure with disproportionately raised creatinine
- Elevated CK
- Myoglobinuria
- **Hypocalcemia (myoglobin binds calcium)**
- Elevated phosphate (released from myocytes)

Causes

- Seizure
- Collapse/coma (e.g. Elderly patients collapses at home, found 8 hours later)
- Ecstasy
- Crush injury
- Mcardle's syndrome
- Drugs: statins

Management

- IV fluids to maintain good urine output
- Urinary alkalinization is sometimes used

Multiple Myeloma: is a neoplasm of the bone marrow plasma cells. The peak incidence is patients aged 60-70 years.

Clinical features

- Bone pain, osteoporosis + pathological fractures (typically vertebral), osteolytic lesions
- Lethargy
- Infection
- Hypercalcemia (see below)
- Renal failure
- Other features: amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity

Diagnosis is based on:

- Monoclonal proteins in the serum and urine (Bence Jones proteins)
- ↑ plasma cells in the bone marrow
- Bone lesions on the skeletal survey
- Other findings on investigations:
    - Rouleaux formation of RBCs on blood film

FYI	Rouleaux are stacks of RBCs which form because of the unique discoid shape of the cells in vertebrate body. The flat surface of the discoid RBCs give them a large surface area to make contact and stick to each other; thus, forming a rouleau. They occur when the plasma protein concentration is high, and because of them the ESR is also increased. This is a non-specific indicator of the presence of disease. Conditions which cause rouleaux formation include infections, Multiple myeloma, inflammatory and connective tissue disorders, and cancers. It also occurs in DM and is one of the causative factors for microvascular occlusion in diabetic retinopathy.

Hypercalcemia in myeloma

- Due primarily to ↑ osteoclastic bone resorption caused by local cytokines released by the myeloma cells
- Other contributing factors include impaired renal function, ↑ renal tubular calcium reabsorption and elevated PTH-rP levels

Part II Tip

Diagnostic criteria: for symptomatic myeloma, asymptomatic myeloma and MGUS

1. **Symptomatic myeloma:**

- Clonal plasma cells >10% on bone marrow biopsy or (in any quantity) in a biopsy from other tissues (plasmacytoma)
- A monoclonal protein (paraprotein) in either serum or urine(except in cases of true non-secretory myeloma)
- Evidence of end-organ damage felt related to the plasma cell disorder (related organ or tissue impairment, ROTI, commonly referred to by the acronym "CRAB"):
  - HyperCalcemia (corrected calcium >2.75 mmol/L)
  - Renal insufficiency attributable to myeloma
- Anemia (hemoglobin <10 g/dL)
- Bone lesions (lytic lesions or osteoporosis with compression fractures)

Note: recurrent infections alone in a patient who has none of the CRAB features is not sufficient to make the diagnosis of myeloma. Patients who lack CRAB features but have evidence of amyloidosis should be considered as amyloidosis and not myeloma. CRAB like abnormalities are common with numerous diseases, and it is imperative that these abnormalities are felt to be directly attributable to the related plasma cell disorder and every attempt made to rule out other underlying causes of anemia, renal failure etc.

2. **Asymptomatic myeloma:**

- Serum paraprotein >30 g/L AND/OR
- Clonal plasma cells >10% on bone marrow biopsy AND
- NO myeloma-related organ or tissue impairment

3. **Monoclonal gammopathy of undetermined significance (MGUS):**

- Serum paraprotein <30 g/L AND
- Clonal plasma cells <10% on bone marrow biopsy AND
- NO myeloma-related organ or tissue impairment

B2-microglobulin is a useful marker of prognosis - raised levels imply poor prognosis. **Low levels of albumin are also associated with a poor prognosis**

International prognostic index

Stage	Criteria	Median survival (months)
I	B2 microglobulin < 3.5 mg/l Albumin > 35 g/l	62
II	Not I or III	45
III	B2 microglobulin > 5.5 mg/l	29

Part II Tip

Initial treatment depends on the patient's age and comorbidities:
< 65 years of age:

- High-dose chemotherapy with hematopoietic stem-cell transplantation
- Prior to stem-cell transplantation, these patients receive an initial course of induction chemotherapy (thalidomide–dexamethasone, bortezomib and lenalidomide–dexamethasone.
- Autologous stem cell transplantation (ASCT), (patient's own stem cells after chemotherapy), is the most common type of stem cell transplantation for multiple myeloma. It is not curative, but does prolong overall survival.
- Allogeneic stem cell transplantation, (transplantation of a healthy person's stem cells into the affected patient), has the potential for a cure, but is only available to a small percentage of patients.

> 65 years old and patients with significant concurrent illness:

- Chemotherapy (Bortezomib) with melphalan and prednisone.

DVT and pulmonary embolism are the major side effects of thalidomide and lenalidomide. Lenalidomide causes more myelosuppression, and thalidomide causes more sedation. Peripheral neuropathy and thrombocytopenia are major side effects of bortezomib

Maintenance therapy: In younger patients, post-ASCT maintenance therapy with thalidomide (this is not licensed for therapeutic use yet, still in trials phase)

Renal failure in multiple myeloma can be acute (reversible) or chronic (irreversible). Acute renal failure typically resolves when the calcium and paraprotein levels are brought under control. Treatment of chronic renal failure is dependent on the type of renal failure and may involve dialysis.

Ewing's Sarcoma

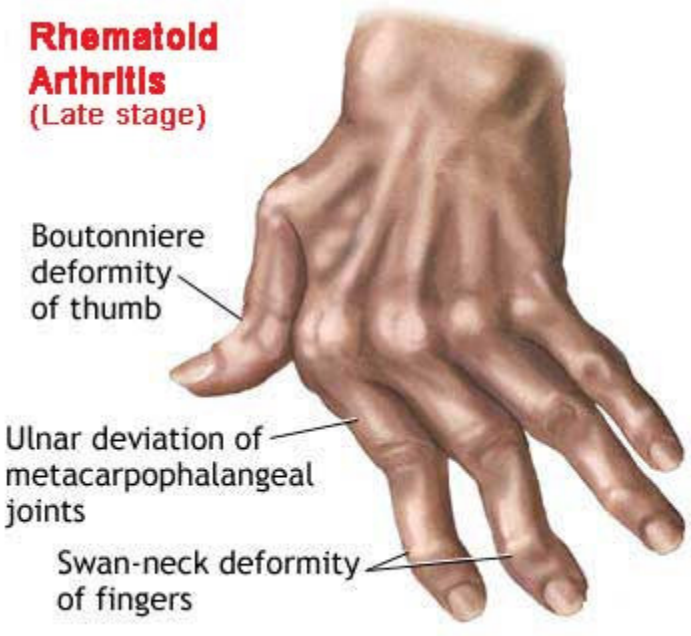
Ewing's Sarcoma is the most lethal malignant primary bone tumor derived from the red bone marrow. It is most common in children and adolescents and rare after the age of 30 years. It has a ♂:♀= 3:2.

Presentation: earliest symptom is pain, which is usually intermittent but becomes increasingly intense. Delay in the diagnosis can occur due to the fact that the clinical picture may be similar to that of acute or chronic osteomyelitis. However, eventually most patients have a large palpable rapidly growing mass, which is tense and tender.

Poor prognostic features:

- ♂
- Age > 12 years
- ↑ LDH
- Anemia
- Poor response to chemotherapy.

RHEUMATOLOGY



Extractable Nuclear Antigens	
Overview • Specific nuclear antigens • Usually associated with being ANA positive	**Examples** • Anti-Ro: Sjogren's syndrome, SLE, congenital heart block • Anti-La: Sjogren's syndrome • Anti-Jo 1: polymyositis • Anti-SCL-70: diffuse cutaneous systemic sclerosis • Anti-centromere: limited cutaneous systemic sclerosis

Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate in the synovium. It is caused by chronic hyperuricemia (uric acid > 450 µmol/l) mostly due to ↓ renal execretion of UA (90%).

↓ Excretion of uric acid	↑ Production of uric acid
• Drugs*: diuretics • Chronic kidney disease • Lead toxicity	• Myeloproliferative/lymphoproliferative disorder • Cytotoxic drugs • Severe psoriasis

*Aspirin 75-150mg should be continued if required for cardiovascular prophylaxis

Lesch-Nyhan syndrome

- Hypoxanthine-guanine phosphoribosyl transferase deficiency
- Inheritance = X-linked recessive
- Features: gout, renal failure, learning difficulties, head-banging

Tophaceous gout:

- Associated with renal impairment and prolonged diuretics use.
- Affected joints are hot swollen and knobby appearance.
- Due to deposition of Na^+ urate in skin and joint.
- X-ray: punched out bony cyst.

Drug causes

- Thiazides, furosemide
- Alcohol
- Cytotoxic agents
- Pyrazinamide

Colchicine is useful in patients with renal impairment who develop gout as NSAIDs are relatively contraindicated. BNF advises to ↓ the dose by up to 50% if creatinine clearance is less than 50 ml/min and to avoid if creatinine clearance is less than 10 ml/min.

Co-codamol 30/500 may be used as an adjunct but would not provide relief as monotherapy.

Prednisolone is an option but not preferred in a diabetic patient

Lithium was actually used to treat gout in the 19th century

Acute management

- NSAIDs
- Intra-articular steroid injection
- Colchicine has a slower onset of action. (main side-effect is diarrhea and ↑ INR with warfarin)
- If the patient is already taking allopurinol it should be continued
- Rasburicase: is a recombinant version of a urate oxidase enzyme given in acute setting, it allows allopurinol to be commenced without worsening of symptoms. Only used when other Rx can not be given

Gout: start allopurinol if ≥ 2 attacks in 12 month period

Allopurinol prophylaxis - see indications below

- Allopurinol should not be started until 2 weeks after an acute attack has settled.
- Initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300 µmol/l
- NSAID or colchicine cover should be used when starting allopurinol

Indications for allopurinol*

- Recurrent attacks - the British Society for Rheumatology recommend '**In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year**'
- Tophi
- Renal disease
- Uric acid renal stones
- Prophylaxis if on cytotoxics or diuretics

Lifestyle modifications

- ↓ alcohol intake and avoid during an acute attack
- Lose weight if obese
- Avoid food high in purines e.g. Liver, kidneys, seafood, oily fish (mackerel, sardines) and yeast products

*patients with Lesch-Nyhan syndrome often take allopurinol for life

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Pseudogout is a form of microcrystal synovitis caused by the deposition of calcium pyrophosphate dihydrate in the synovium

Features

- Knee, wrist and shoulders most commonly affected
- X-ray: chondrocalcinosis **(linear calcification of the articular cartilage)**
- Joint aspiration: weakly-positively birefringent rhomboid shaped crystals

Risk factors

- **Hyperparathyroidism**
- **Hypothyroidism**
- Hemochromatosis
- **Acromegaly**
- **↓ magnesium, ↓ phosphate**
- Wilson's disease

Investigations:

- Transferrin saturation (may indicate hemochromatosis, a recognised cause of pseudogout)

Management:

- Aspiration of joint fluid, to exclude septic arthritis and show weakly-positively birefringent brick shaped crystals
- NSAIDs or intra-articular, intra-muscular or oral steroids as for gout

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Rheumatoid Arthritis:

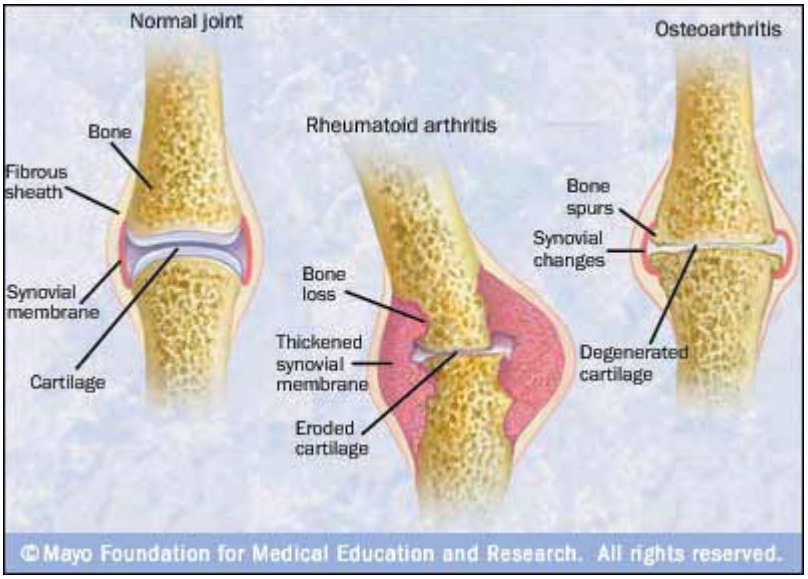
Epidemiology

- Peak onset = 30-50 years, although occurs in all age groups
- ♀:♂ ratio = 3:1
- Prevalence in UK = 1%
- Some ethnic differences e.g. High in native Americans
- Associated with HLA-DR4 (especially felty's syndrome)

American College of Rheumatology criteria

- Requires 4 of the following 7 criteria
- Sensitivity = 92%, specificity = 89%

1. Morning stiffness > 1 hr (for at least 6 weeks)
2. Soft-tissue swelling of 3 or more joints (for at least 6 weeks)
3. Swelling of PIP, MCP or wrist joints (for at least 6 weeks)
4. Symmetrical arthritis
5. Subcutaneous nodules
6. Rheumatoid factor positive
7. Radiographic evidence of erosions or periarticular osteopenia



Rheumatoid arthritis - TNF is key in pathophysiology

Anti-cyclic citrullinated peptide antibody may be detectable up to 10 years before the development of rheumatoid arthritis. It may therefore play a key role in the future of rheumatoid arthritis, allowing early detection of patients suitable for aggressive anti-TNF therapy. It has sensitivity similar to rheumatoid factor (70-80%, see below) with a much higher specificity of 90-95%.

NICE recommends that patients with suspected rheumatoid arthritis who are rheumatoid factor negative should be tested for **anti-CCP antibodies**.

Early x-ray findings

- Loss of joint space (seen in both RA and osteoarthritis)
- Juxta-articular osteoporosis
- Soft-tissue swelling

Late x-ray findings

- Periarticular erosions (osteopenia and osteoporosis)
- Subluxation

A number of features have been shown to predict a poor prognosis in patients with rheumatoid arthritis, as listed below

Poor prognostic features

- Rheumatoid factor positive
- Poor functional status at presentation
- HLA DR4
- X-ray: early erosions (in < 2 years)
- Extra articular features e.g. Nodules
- ♀ sex
- Insidious onset
- Anti-CCP antibodies

In terms of gender there seems to be a split in what the established sources state is associated with a poor prognosis. However both the American College of Rheumatology and the recent NICE guidelines (which looked at a huge number of prognosis studies) seem to conclude that female gender is associated with a poor prognosis

Rheumatoid arthritis: patients have an increased risk of IHD

Extra-articular complications occur in patients with rheumatoid arthritis (RA):

- Respiratory: pulmonary fibrosis, pleural effusion, pulmonary nodules, bronchiolitis obliterans, methotrexate pneumonitis, pleurisy
- Ocular: keratoconjunctivitis sicca (most common), episcleritis, scleritis, corneal ulceration, keratitis, steroid-induced cataracts, chloroquine retinopathy
- Osteoporosis
- ISCHEMIC heart disease: RA carries a similar risk to T2DM
- Increased risk of infections
- Depression

Less common

- Felty's syndrome (RA + splenomegaly + low white cell count)
- Amyloidosis

Proteus mirabilis is a (G-ve rod), causes UTI → predisposes susceptible patients to RA

Management of rheumatoid arthritis (RA) has been revolutionized by the introduction of disease-modifying therapies in the past decade. NICE has issued a number of technology appraisals on the newer agents and released general guidelines in 2009.

Patients with evidence of joint inflammation should start a combination of disease-modifying drugs (DMARD) as soon as possible. Other important treatment options include analgesia, physiotherapy and surgery.

Initial therapy

- In the 2009 NICE guidelines it is recommend that patients with newly diagnosed active RA start a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids)

DMARDs

- Methotrexate is the most widely used DMARD. Monitoring FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis. Other important side-effects include pneumonitis
- Sulfasalazine
- Hydroxychloroquine } Safe in pregnancy
- Leflunomide

In Pregnancy
Methotrexate and NSAIDs are absolutely contraindicated **Azathiopurine can be used if sulfasalazine and hydroxychloroquine are not controlling**

TNF-inhibitors

- The current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- Etanercept: subcutaneous administration, can cause demyelination
- Infliximab: intravenous administration, risks include reactivation of tuberculosis
- Adalimumab: subcutaneous administration

} Stop 2-4 weeks before any major surgery

Rituximab

- Anti-CD20 monoclonal antibody, results in B-cell depletion
- Two 1g intravenous infusions are given two weeks apart
- Infusion reactions are common

Abatacept

- Fusion protein that modulates a key signal required for activation of T lymphocytes
- Leads to ↓ T-cell proliferation and cytokine production
- Given as an infusion

Respiratory Problems in Rheumatoid Arthritis

: A variety of respiratory problems may be seen in patients with rheumatoid arthritis:

- Pulmonary fibrosis
- Pleural effusion
- Pulmonary nodules
- Bronchiolitis obliterans
- Complications of drug therapy e.g. Methotrexate pneumonitis
- Pleurisy
- Caplan's syndrome - massive fibrotic nodules with occupational coal dust exposure
- Infection (possibly atypical) secondary to immunosuppression

---

Adult Still's Disease:

is a form of rheumatoid arthritis typically affects 16-35 year olds

Features:

- Arthralgia
- Fever (noticeable at afternoon and evening)
- Elevated serum ferritin

- Rash: salmon-pink, maculopapular, pruritic
- Pyrexia
- Lymphadenopathy
- RF and ANA negative (but ANA 25% positive). ↑ ESR and CRP
- Leukocytosis and thrombocytosis

Management:
- NSAIDs
- Steroids
- Methotrexate

Septic Arthritis

Joint aspiration is mandatory in all patients with a hot, swollen joint to rule out septic arthritis. If this was excluded then intra-articular or system steroid therapy may be considered

Overview
- Most common organism overall is *Staphylococcus aureus*
- In young adults who are sexually active *Neisseria gonorrhea* should also be considered
- WBC > 50 x 10^9/L or > 75% of baseline – neutrophils

Management
- Synovial fluid should be obtained before starting treatment
- Intravenous antibiotics which cover gram-positive cocci are indicated. The BNF currently recommends **flucloxacillin + fusidic acid** or clindamycin if penicillin allergic
- Antibiotic treatment is normally be given for several weeks (BNF states 6-12 weeks)
- Needle aspiration should be used to decompress the joint
- Surgical drainage may be needed if frequent needle aspiration is required

Osteoarthritis:

The trapeziometacarpal joint (base of thumb) is the most common site of hand osteoarthritis

NICE published guidelines on the management of osteoarthritis (OA) in 2008
- All patients should be offered help with weight loss, given advice about local muscle strengthening exercises and general aerobic fitness
- Paracetamol and topical NSAIDs are first-line analgesics. Topical NSAIDs are indicated only for OA of the knee or hand
- Second-line treatment is oral NSAIDs/cox-2 inhibitors, opioids, capsaicin cream and intra-articular corticosteroids. A proton pump inhibitor should be co-prescribed with either drug. These drugs should be avoided if the patient takes aspirin
- Non-pharmacological treatment options include supports and braces, tens and shock absorbing insoles or shoes
- If conservative methods fail then refer for consideration of joint replacement

What is the role of glucosamine?
- Normal constituent of glycosaminoglycans in cartilage and synovial fluid
- A systematic review of several double blind RCTs of glucosamine in knee osteoarthritis reported significant short-term symptomatic benefits including significantly ↓ joint space narrowing and improved pain scores
- More recent studies have however been mixed

- The 2008 NICE guidelines suggest it is **NOT RECOMMENDED**
- A 2008 drug and therapeutics bulletin review advised that whilst glucosamine provides modest pain relief in knee osteoarthritis it should not be prescribed on the NHS due to limited evidence of cost-effectiveness

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Reactive Arthritis is one of the HLA-B27 associated seronegative spondyloarthropathies. It encompasses **Reiter's syndrome, a term which described a classic triad of urethritis, conjunctivitis and arthritis following a dysenteric illness** during the Second World War. Later studies identified patients who developed symptoms following a sexually transmitted infection (post-STI, now sometimes referred to as sexually acquired reactive arthritis, SARA)

"the patient can't see, can't pee, can't bend the knee"

Features

- Typically develops within 4 weeks of initial infection - symptoms generally last around 4-6 months
- Arthritis is typically an **asymmetrical oligoarthritis** of lower limbs
- May present as monoarthritis e.g. Knee
- Symptoms of urethritis
- Eye: conjunctivitis (seen in 50%), anterior uveitis
- Skin: circinate balanitis (painless vesicles on the coronal margin of the prepuce), keratoderma blenorrhagica (waxy yellow/brown papules on palms and soles)

Around 25% (15-50%) have recurrent episodes whilst 10% (15-30%) develop chronic disease.

Ankylosing spondylitis develop in upto 50% of HLA B27 +ve patients

The American College of Rheumatology now define reactive arthritis as an episode of peripheral arthritis lasting for greater than 1 month associated with urethritis/cervicitis or diarrhea

Epidemiology

- Post-STI form much more common in men (e.g. 10:1)
- Post-dysenteric form equal sex incidence with better prognosis

Organisms often responsible for post-dysenteric form	Organisms often responsible for post-STI form
• *Shigella* flexneri • *Salmonella typhimurium* • *Salmonella* enteritidis • *Yersinia enterocolitica* • *Campylobacter*	• *Chlamydia trachomatis*

Management

- Symptomatic: analgesia, NSAIDs, intra-articular steroids
- Sulfasalazine and methotrexate are sometimes used for persistent disease
- Symptoms rarely last more than 12 months

Palindromic Arthritis: (From the Greek "palindromos" means to come and go)

Characterized by:

- Rare type of recurrent inflammatory arthritis that causes sudden inflammation in one or several joints (pain, swelling and erythema) followed by complete recovery with no permanent damage.
- Affects articular or periarticular areas, any joint could be affected but mostly large joints
- Lasts < 72 hours before recovering completely
- ♂=♀ - age 20-50 years.
- May progress to RA: incidence of RA may ↑ when RF is present
- Anti-CCP and antikeratin antibodies (AKA) are present in a high proportion of patients

The most common cause of recurrent or relapsing arthritis: Crystal Arthritis (Gout & Pseudogout)

Recent-Onset Arthritis can be due to parvovirus-induced arthritis

- Exposure to children with recent febrile illness is known risk
- Affects ♀>♂ - mostly women with contact to children (at home or at work)
- Small hands joints, wrists, elbows, hips, knees, and feet are each affected in > 50% of cases.
- Detection of IgM antibody, produced only in early disease, is a marker of recent infection and therefore strong evidence in favor of parvovirus being the cause of recent-onset arthritis.

Ankylosing Spondylitis

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathies. It typically presents in ♂s (sex ratio 5:1) aged 20-30 years old. It has **polygenic inheritance**.

HLA-B27 is of little use in making the diagnosis as it is positive in:

- 90% of patients with ankylosing spondylitis
- 10% of normal patients

Features

- Typically a young man who presents with lower back pain and stiffness
- Stiffness is usually worse in morning and improves with activity
- The patient may experience pain at night which improves on getting up
- Peripheral arthritis (25%, more common if ♀)

Features - the 'A's

- **Apical fibrosis (CXR)**
- **Anterior uveitis**
- **Aortic regurgitation**
- **Achilles tendonitis**
- **AV node block**
- **Amyloidosis**
- **And cauda equina syndrome**

Clinical examination

- Reduced lateral flexion
- Reduced forward flexion - Schober's test - a line is drawn 10 cm above and 5 cm below the back dimples (dimples of Venus). The distance between the two lines should increase by more than 5 cm when the patient bends as far forward as possible
- Reduced chest expansion

↓ Lateral flexion of the lumbar spine is one of the earliest signs of ankylosing spondylitis. There tends to be a loss of lumbar lordosis and an accentuated thoracic kyphosis in patients with ankylosing spondylitis

X-ray of the sacro-iliac joints is the most useful investigation for diagnosis and monitoring, but changes may not be seen for many years after the onset of symptoms

X-rays are often normal early in disease, later changes include:

- Sacroilitis: subchondral erosions, sclerosis
- Squaring of lumbar vertebrae
- 'Bamboo spine' (late & uncommon)

- CXR: apical fibrosis

Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints

Management

- NSAIDs
- Physiotherapy
- Sulphasalazine may be useful if there is peripheral joint involvement - doesn't improve spinal mobility
- TNF-α blockers such as etanercept and adalimumab are increasingly used. This approach for severe ankylosing spondylitis was supported by NICE in 2008

Seronegative Spondyloarthropathies

Common features

- Associated with HLA-B27
- **Rheumatoid factor negative - hence 'seronegative'**
- Peripheral arthritis, usually asymmetrical
- Sacroilitis
- Enthesopathy: e.g. Achilles tendonitis, plantar fasciitis
- Extra-articular manifestations: uveitis, pulmonary fibrosis (upper zone), amyloidosis, aortic regurgitation

Spondyloarthropathies

- Ankylosing spondylitis
- Psoriatic arthritis
- Reiter's syndrome (including reactive arthritis)
- Enteropathic arthritis (associated with IBD)

Pseudoxanthoma Elasticum

is an inherited condition (usually autosomal recessive*) characterized by an abnormality in elastic fibers

Features

- Retinal angioid streaks
- 'Plucked chicken skin' appearance - small yellow papules on the neck, antecubital fossa and axillae
- Cardiac: mitral valve prolapse, ↑ risk of ischemic heart disease
- Gastrointestinal hemorrhage

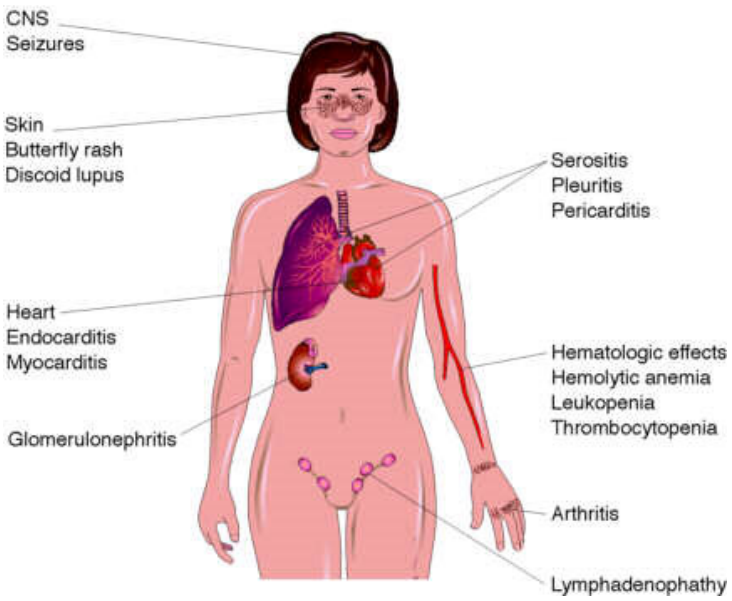
*there are reports of autosomal dominant inheritance in a minority of cases

Systemic Lupus Erythematosus (SLE)

Low levels of C4a and C4b have been shown to be associated with ↑ risk of developing systemic lupus erythematous

Epidemiology

- Much more common in ♀s (F:M = 9:1)
- More common in Afro-Caribbeans* and Asian communities
- Onset is usually 20-40 years
- Incidence has risen substantially during the past 50 years (3 fold using American College of Rheumatology criteria)



Pathophysiology

- Autoimmune disease
- Associated with HLA B8, DR2, DR3
- Thought to be caused by immune system dysregulation leading to immune complex formation
- Immune complex deposition can affect any organ; skin, joints, kidneys and brain most commonly affected

*It is said the incidence in black Africans is much lower than in black Americans - the reasons for this are unclear

Immunology

- ANA positive (**99% SENSITIVE**)
- 20% are rheumatoid factor positive
- Anti-dsDNA: **HIGHLY SPECIFIC** (> 99%), but less sensitive (70%)
- Anti-Smith: **MOST SPECIFIC** (> 99%), sensitivity (30%)
- Antihistone positive in drug indiced lupus
- Congenital ↓ C4 is a predisposing factor for SLE

SLE: C3 & C4 low

Monitoring

- ESR: during active disease the **CRP** is characteristically **normal** - a raised CRP may indicate underlying infection
- Complement levels (C3, C4) are low during active disease (formation of complexes leads to consumption of complement) ↓ C4 is early marker for disease activity
- Anti-DsDNA titers: used for disease monitoring disease activity (but not present in all patients)

SLE and Pregnancy: Unlike many autoimmune diseases systemic lupus erythematous **(SLE) often becomes worse during pregnancy and the puerperium**

- Risk of maternal autoantibodies crossing placenta
- Leads to condition termed neonatal lupus erythematous
- Neonatal complications include congenital heart block, it is strongly associated with anti-Ro (SSA) antibodies

Drug-induced Lupus not all the typical features of systemic lupus erythematosus are seen, with renal and nervous system involvement being unusual. It usually resolves on stopping the drug

Features

- Arthralgia
- Myalgia
- Skin (e.g. malar rash) and pulmonary involvement (e.g. pleurisy) are common
- ANA positive in 100%, dsDNA negative
- Anti-Ro, anti-Smith positive in around 5%

Causes

- Anti-epileptics: phenytoin
- Chlorpromazine
- Hydralazine
- Isoniazid
- Minocycline
- **Procainamide**

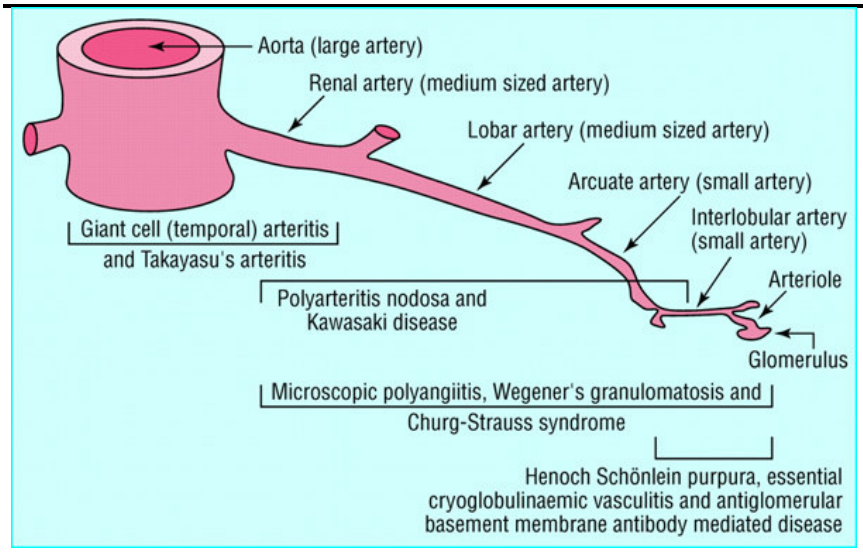
Discoid Lupus Erythematous is a benign disorder generally seen in younger ♀s. It very rarely progresses to systemic lupus erythematosus (in less than 5% of cases). Discoid lupus erythematous is characterized by **follicular keratin plugs** and is thought to be autoimmune in etiology

Features

- Erythematous, raised rash, sometimes scaly
- May be photosensitive
- More common on face, neck, ears and scalp
- Lesions heal with atrophy, scarring (may cause scarring alopecia), and pigmentation

Management

- Topical steroid cream
- Oral antimalarials may be used second-line e.g. Hydroxychloroquine
- Avoid sun exposure



Vasculitis of large-sized blood vessel
Giant cell (temporal) arteritis
Takayasu arteritis

Vasculitis of medium- and small-sized blood vessel
Polyarteritis nodosa
Churg-Strauss syndrome
Wegener's granulomatosis
Kawasaki disease

Vasculitis affecting predominantly small-sized blood vessels
Microscopic polyangiitis
Henoch-Schonlein Syndrome
Essential cryoglobulinemic vasculitis
Cutaneous leukocytoclastic angiitis

Miscellaneous conditions
Buerger's disease
Cogan Syndrome
Behçet disease

Secondary vasculitis
Infection-related vasculitis
Vasculitis secondary to connective tissue disease
Drug-hypersensitivity-related vasculitis
Malignancy-related vasculitis
Hypocomplementemic urticarial vasculitis
Post-organ-transplant vasculitis

Temporal Arteritis is large vessel vasculitis which overlaps with polymyalgia rheumatica (PMR). Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others

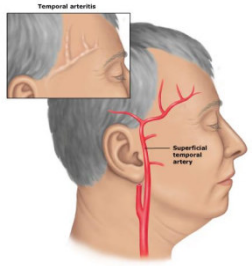
Intermittent headaches and lethargy with ↑ ESR

Features

- Typically patient > 60 years old
- Usually rapid onset (e.g. < 1 month)
- Headache (found in 85%)
- Jaw claudication (65%)
- Tender, palpable temporal artery
- Features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- Also lethargy, depression, low-grade fever, anorexia, night sweats
- Associated with sudden blindness due to the involvement of anterior ischemic optic neuropathy

Investigations

- ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
- Temporal artery biopsy: skip lesions may be present
- Note CK and EMG normal
- ↓ CD8+ T cells



Treatment

- Should be started immediately with high dose steroids (e.g. prednisolone 1mg/kg/day) to ↓ the chance of visual loss. there should be a dramatic response, if not the diagnosis should be reconsidered
- Urgent ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible

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Takayasu disease (TD): is a continuous or patchy granulomatous inflammatory process involving macrophages, lymphocytes, and multinucleated giant cells which cause progressive occlusive disease of the aorta and its branches.

- Very rare in the Western world with an annual incidence of between 2 and 3 per million.
- Approximately 80% of patients are women, and the mean age of onset is 30 years.
- Presentation may be with constitutional symptoms such as fever, malaise, and weight loss; neurological symptoms such as transient ischemic attacks; or vascular symptoms such as claudication.
- Cardiac features include angina, heart failure, and aortic regurgitation.
- Renal manifestations may include mesangial proliferative glomerulonephritis.
- Corticosteroids with the addition of steroid sparing second agents such as methotrexate or azathioprine are the mainstay of therapy.
- With good care, 15-year survival rates approach 90%.

Polyarteritis Nodosa (PAN) is a **vasculitis affecting medium-sized arteries** with necrotizing inflammation leading to aneurysm formation. PAN is more common in middle-aged men and is associated with hepatitis B infection

Features

- Fever, malaise, arthralgia
- **Hypertension**
- Mononeuritis multiplex, sensorimotor polyneuropathy
- Hematuria, renal failure
- Testicular pain
- Abdominal pain (e.g. From mesenteric ischemia)
- Perinuclear-antineutrophil cytoplasmic antibodies (pANCA) are found in around 20% of patients with 'classic' PAN

Diagnostic Criteria: 3 of the 10 following signs known as the 1990 ACR (American College of Rheumatology):

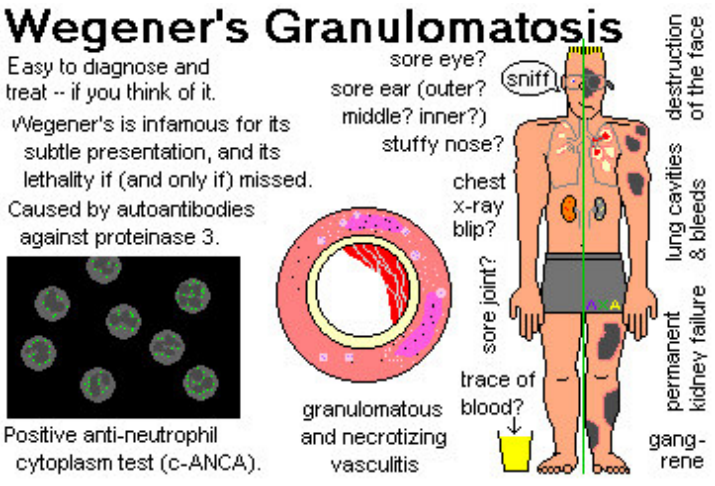
1. Weight loss ≥ to 4.5 kg.
2. Livedo reticularis
3. Testicular pain or tenderness. (Occasionally, a site biopsied for diagnosis).
4. Muscle pain, weakness, or leg tenderness.
5. Nerve disease (either single or multiple).
6. Diastolic BP > 90mmHg
7. ↑ Kidney function tests (BUN and Creatinine)
8. Hepatitis B positive (surface antigen or antibody).
9. Abnormal arteriogram (angiogram)
10. Biopsy of small/medium size artery (typically inflamed arteries).

Wegener's Granulomatosis is an autoimmune condition associated with a necrotizing granulomatous vasculitis, affecting both the upper and lower respiratory tract as well as the kidneys.

The combination of pulmonary and renal involvement combined with a history of chronic sinusitis points towards a diagnosis of Wegener's granulomatosis

Features

- Upper respiratory tract: epistaxis, sinusitis, nasal crusting
- Lower respiratory tract: dyspnea, hemoptysis
- Glomerulonephritis ('pauci-immune', 80% of patients)
- Saddle-shape nose deformity
- Also: vasculitic rash, eye involvement (e.g. Proptosis), cranial nerve lesions



Investigations

- cANCA positive in > 90%, pANCA positive in 25%
- Chest x-ray: wide variety of presentations, including cavitating lesions

Management:

- Steroids
- Cyclophosphamide (90% response)
- Plasma exchange
- Median survival = 8-9 years

Churg-Strauss Syndrome is an ANCA associated **small-medium vessel vasculitis**

Asthma + eosinophilia + nerve lesion = CSS

Features

- Asthma and sometimes pulmonary esinophilic infiltrate
- Blood eosinophilia (e.g. > 10%)
- Paranasal sinusitis
- Mononeuritis multiplex
- **pANCA positive in 60% - Anti myeloperoxidase antibody**

Leukotriene receptor antagonists may precipitate the disease

Henoch-Schonlein purpura (HSP) is an IgA mediated small vessel vasculitis. There is a degree of overlap with IgA nephropathy (Buerger's disease). HSP is usually seen in children following an infection. Characterized by **(Features):**

- Palpable purpuric rash (with localized edema) over buttocks, extensor surfaces of arms and legs
- Abdominal pain, non-bloody diarrhea.
- Polyarthritis
- Features of IgA nephropathy may occur e.g. Hematuria, renal failure

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Thrombangiitis Obliterans (Buerger's disease) is a disease of **small and medium-sized arteries and veins** resulting in inflammation and ulceration.

- No excessive atheroma
- Does not involve the coronary arteries like atherosclerosis.
- Occurs mainly in cigarette smokers; it has not been documented in non-smokers.
- Patients present with symptoms of arterial ischemia.
- Migratory phlebitis in the superficial vein is present in 40% of cases.
- The disease progresses proximally, resulting in gangrene of the digits.
- Diagnosis is usually clinical. Arteriogram is also of benefit and will show occlusion of distal arteries of the hands and feet.
- Treatment is supportive and patients should stop smoking.

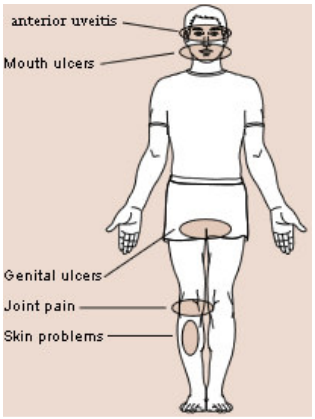
Behcet's Syndrome is a complex multisystem disorder associated with presumed autoimmune mediated inflammation of the **arteries and veins**. The precise etiology has yet to be elucidated however. **The classic triad of symptoms is oral ulcers, genital ulcers and anterior uveitis**

Epidemiology

- More common in the eastern Mediterranean (e.g. Turkey)
- More common in men (complicated gender distribution which varies according to country. Overall, Behcet's is considered to be more common and more severe in men)
- Tends to affect young adults (e.g. 20 - 40 years old)
- Associated with HLA B51 and MICA6 allele
- C. 30% of patients have a positive family history

Features

- Classically: 1) oral ulcers 2) genital ulcers 3) anterior uveitis
- Thrombophlebitis
- Arthritis
- Neurological involvement (e.g. Aseptic meningitis)
- GI: abdo pain, diarrhea, colitis
- Erythema nodosum, DVT



Ocular involvement is the most feared complication of Behcet's syndrome. Conjunctivitis is seen rarely and is much less common than anterior uveitis. Other ocular problems seen include retinal vasculitis, iridocyclitis and chorioretinitis

Diagnosis

- No definitive test
- Diagnosis based on clinical findings
- Positive pathergy test is suggestive (puncture site following needle prick becomes inflamed with small pustule forming)

Mangement:

- Steroids
- Azathioprine

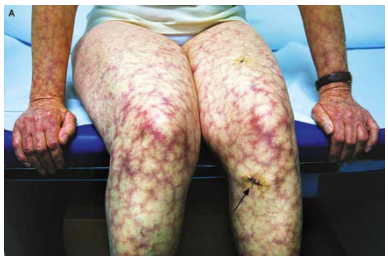
Antiphospholipid syndrome: (paradoxically) prolonged APTT + low platelets

Antiphospholipid Syndrome (Hughes syndrome) is an acquired disorder characterized by a predisposition to **both venous and arterial thromboses**, recurrent fetal loss and thrombocytopenia. It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

A key point for the exam is to appreciate that antiphospholipid syndrome causes a **paradoxical rise in the APTT**. This is due to an ex-vivo reaction of the lupus anticoagulant autoantibodies with phospholipids involved in the coagulation cascade.

Features

- Venous/arterial thrombosis
- Recurrent fetal loss
- Livedo reticularis
- Thrombocytopenia
- Prolonged APTT
- Other features: pre-eclampsia, pulmonary hypertension



Livedo reticularis

Associations other than SLE

- Other autoimmune disorders
- Lymphoproliferative disorders
- Phenothiazines (rare)

Management - based on BCSH guidelines

- Initial venous thromboembolic events: evidence currently supports use of warfarin with a target INR of 2-3 for 6 months
- Recurrent venous thromboembolic events: lifelong warfarin; if occurred whilst taking warfarin then ↑ target INR to 3-4
- Arterial thrombosis should be treated with lifelong warfarin with target INR 2-3

In pregnancy the following complications may occur:

- Recurrent miscarriage
- IUGR
- Pre-eclampsia
- Placental abruption
- Pre-term delivery
- Venous thromboembolism

Management

- Low-dose aspirin should be commenced once the pregnancy is confirmed on urine testing
- Low molecular weight heparin once a fetal heart is seen on ultrasound. This is usually discontinued at 34 weeks gestation
- **These interventions ↑ the live birth rate seven-fold**

Polymyalgia Rheumatica:

Pathophysiology

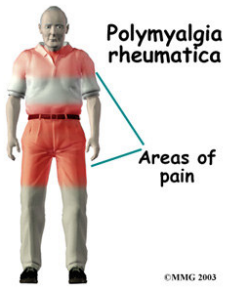
- Overlaps with temporal arteritis
- Histology shows vasculitis with giant cells, characteristically 'skips' certain sections of affected artery whilst damaging others
- Muscle bed arteries affected most in polymyalgia rheumatica

Features

- Typically patient > 60 years old
- Usually rapid onset (e.g. < 1 month)
- Aching, **morning stiffness** in proximal limb muscles **(not weakness)**
- Also mild polyarthralgia, lethargy, depression, low-grade fever, anorexia, night sweats

Investigations

- ESR > 40 mm/hr
- Note CK and EMG normal
- ↓ CD8+ T cells



Treatment

- Prednisolone e.g. 15mg/od - dramatic response

Anti-ribonuclear protein (anti-RNP) = mixed connective tissue disease

Features of SLE, systemic sclerosis and polymyositis

Cryoglobulinemia: immunoglobulins which undergo reversible precipitation at 4°C, dissolve when warmed to 37°C. One third of cases are idiopathic

Three types

- Type I (25%): monoclonal
- Type II (25%): mixed monoclonal and polyclonal: usually with RF
- Type III (50%): polyclonal: usually with RF

Type I

- Monoclonal - IgG or IgM
- Associations: multiple myeloma, Waldenström macroglobulinemia

Type II

- Mixed monoclonal and polyclonal: usually with RF
- Associations: hepatitis C, RA, Sjogren's, lymphoma

Type III

- Polyclonal: usually with RF
- Associations: RA, Sjogren's

Symptoms (if present in high concentrations)

- Raynaud's only seen in type I
- Cutaneous: vascular purpura, distal ulceration, ulceration
- Arthralgia
- Renal involvement (diffuse mesangiocapillary glomerulonephritis)

Tests

- Low complement (esp. C4)
- High ESR

Treatment

- Immunosuppression
- Plasmapheresis

Raynaud's Phenomena may be primary (Raynaud's disease) or secondary (Raynaud's phenomenon). Raynaud's disease typically presents in young women (e.g. 30 years old) with symmetrical attacks

Factors suggesting underlying connective tissue disease

- Onset after 40 years
- Unilateral symptoms
- Rashes
- Presence of autoantibodies
- Digital ulcers, calcinosis
- Very rarely: chilblains (pernio) are itchy, painful purple swellings which occur on the fingers and toes after exposure to the cold. They are occasionally associated with underlying connective tissue disease but this is rare
- Recurrent miscarriages: This indicates SLE or antiphospholipid syndrome.

Secondary causes

- Connective tissue disorders: **scleroderma (most common)**, rheumatoid arthritis, SLE with bilateral symptoms
- Leukemia
- Type I cryoglobulinemia, cold agglutinins
- Use of vibrating tools
- Drugs: oral contraceptive pill, ergot
- Cervical rib

Management

- Calcium channel blockers
- IV prostacyclin infusions

Morphea is a form of localized scleroderma that may be circumscribed or generalized.

- In circumscribed morphea, there may be just one or two lesions with no generalized spread.
- Changes often begin with small, violaceous, or erythematous skin lesions, which enlarge and progress to firm hidebound skin with a variable degree of hypo- or hyperpigmentation.
- Lesions eventually settle into a waxy, white appearance with subsequent atrophy.
- Lesions vary in diameter between 1 and 10 cm.
- Condition generally resolves within 3-5 years, although sometimes a patch may persist for over 25 years.
- Auto-antibodies such as anti-nuclear antibody (ANA) are only rarely positive in localized forms of scleroderma, as against systemic subtypes where a positive ANA is one of the hallmarks of the disease.

Psoriatic Arthropathy correlates poorly with cutaneous psoriasis and often precedes the development of skin lesions. Around 10% of patients with skin lesions develop an arthropathy with ♂s and ♀s being equally affected

Types*

- Rheumatoid-like polyarthritis: (30-40%, most common type)
- Asymmetrical oligoarthritis: typically affects hands and feet (20-30%)
- Sacroilitis
- DIP joint disease = arthropathy (10%)
- Arthritis mutilans (severe deformity fingers/hand, 'telescoping fingers')

Management

- Treat as rheumatoid arthritis, but better prognosis

*Until recently it was thought asymmetrical oligoarthritis was the most common type, based on data from the original 1973 Moll and Wright paper.

Dactylitis describes the inflammation of a digit (finger or toe).

Causes include:

- Spondyloarthritis: e.g. Psoriatic and reactive arthritis
- Sickle-cell disease
- Other rare causes include tuberculosis, sarcoid and syphilis

Systemic Sclerosis is a condition of unknown etiology characterized by hardened, sclerotic skin and other connective tissues. It is four times more common in ♀s

There are three patterns of disease:

1. Limited cutaneous systemic sclerosis:

- Raynaud's may be first sign
- Scleroderma affects face and distal limbs predominately
- Associated with anti-centromere antibodies
- CREST syndrome is a subtype of limited cutaneous systemic sclerosis: **C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasia. In CREST **MALABSORPTION** can develop secondary to bacterial overgrowth of the sclerosed small intestine. Unfortunately pulmonary hypertension is one of the more common late complications seen in such patients.

2. Diffuse cutaneous systemic sclerosis:

- Scleroderma affects trunk and proximal limbs predominately
- Associated with SCL-70 antibodies
- Hypertension, lung fibrosis and renal involvement seen
- Poor prognosis

3. Scleroderma (without internal organ involvement):

- Tightening and fibrosis of skin
- May be manifest as plaques (morphoea) or linear

Antibodies

- ANA positive in 90%
- RF positive in 30%
- Anti-SCL-70 antibodies associated with diffuse cutaneous systemic sclerosis
- Anti-centromere antibodies associated with limited cutaneous systemic sclerosis

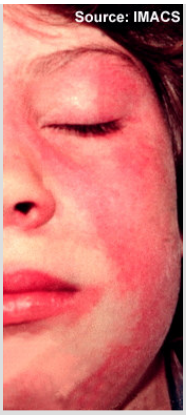
Management:

- Topical treatment for skin changes do not alter the disease course, but may improve pain and ulceration.
    - NSAIDs
    - Limited benefit from steroids
    - Episodes of Raynaud's sometimes respond to nifedipine or other calcium channel blockers. Dual endothelin-receptor antagonist (bosentan) may be beneficial.
    - Severe digital ulceration may respond to prostacyclin analogue iloprost
    - The skin tightness may be treated systemically with methotrexate and ciclosporin
- Scleroderma renal crisis: benefit fro ACE-I to control BP and delay progression to CRF
- Active alveolitis is often treated with pulses of cyclophosphamide, often together with a small dose of steroids. The benefit of this intervention is modest

Dermatomyositis:

Overview

- Inflammatory disorder causing symmetrical, proximal muscle weakness and characteristic skin lesions
- May be idiopathic or associated with connective tissue disorders or underlying malignancy (found in 20-25% - more if old patient)
- Polymyositis is a variant of the disease where skin manifestations are not prominent



Malar and facial erythema. Acute onset of confluent macular erythema in a periorbital and malar distribution with extension to the chin (Heliotrope rash) in a girl with juvenile dermatomyositis. Note the perioral sparing

Skin features

- Photosensitive
- Macular rash over back and shoulder
- Heliotrope rash over cheek
- Gottron's papules - roughened red papules over extensor surfaces of fingers
- Nail fold capillary dilatation

Other features

- Proximal muscle weakness +/- tenderness
- Raynaud's
- Respiratory muscle weakness
- Interstitial lung disease: e.g. Fibrosing alveolitis or organizing pneumonia
- Dysphagia, dysphonia

Investigations:

- ↑ CK
- EMG
- Muscle biopsy
- Anti-jo-1 antibodies are not commonly seen in dermatomyositis - they are more common in polymyositis where they are seen in a pattern of disease associated with lung involvement, raynaud's and fever
- ANA positive in 60%
- Screen for malignancy by U/S abdomen + pelvis-(♀)/+PSA(♂) – CT chest might be needed.

Management:

- Prednisolone

Familial Mediterranean Fever (FMF, also known as recurrent polyserositis) is an autosomal recessive disorder which typically presents by the second decade (90% have their first attacks before the age of 18 years). It is more common in people of **Turkish**, Armenian and Arabic descent

Features - attacks typically last 1-3 days

- Pyrexia (on-off)
- Constipation/Diarrhea may occur with or after the fever
- Abdominal pain (due to peritonitis) – many times appendectomy scar is seen due to multiple admissions due to abdominal pain
- Pleurisy

- Pericarditis
- Arthritis
- Nephrotic syndrome due to renal amyloidosis (that might even need transplantation)
- Erysipeloid rash on lower limbs

Management

- Attacks are self-limiting, and require analgesia
- Colchicine may ↓ attack frequency.

Relapsing Polychondritis (RP) is an inflammatory condition that involves cartilaginous structures, predominantly those of the pinna, nasal septum and larynx.

- ♂=♀ - Can occur at any age, but mostly in the fifth decade (40s of age).
- Symptoms depend on the area of the body affected.
- General symptoms include intermittent fever and weight loss, but other more specific symptoms include sudden onset of ear pain with an inability to sleep on the affected side, diminished hearing, monoarthritis or polyarthritis, back pain, myalgias, mild epistaxis, saddle-shaped nose, redness of the eyes indicative of conjunctivitis, episcleritis and/or scleritis, hoarseness of the voice and recurrent respiratory infections.
- No specific diagnostic laboratory findings in patients with RP but the non-specific indicators of inflammation (ESR, CRP) are often elevated.
- No specific therapy exists for RP but the goal of treatment is to control the patient symptoms and to preserve the integrity of the affected cartilaginous structures.
- The mainstay of treatment is **systemic corticosteroids**. It is important in these patients to investigate for the presence of other concurrent autoimmune diseases

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Sjogren's syndrome is an autoimmune disorder affecting exocrine glands resulting in dry mucosal surfaces. It may be primary (PSS) or secondary to rheumatoid arthritis or other connective tissue disorders, where it usually develops around 10 years after the initial onset. Sjogren's syndrome is much more common in ♀s (ratio 9:1). There is a marked ↑ risk of lymphoid malignancy (40-60 folds)

Features

- Dry eyes: keratoconjunctivitis sicca
- Dry mouth
- Vaginal dryness
- Arthralgia
- Raynaud's, myalgia
- Sensory polyneuropathy
- Renal tubular acidosis (usually subclinical)

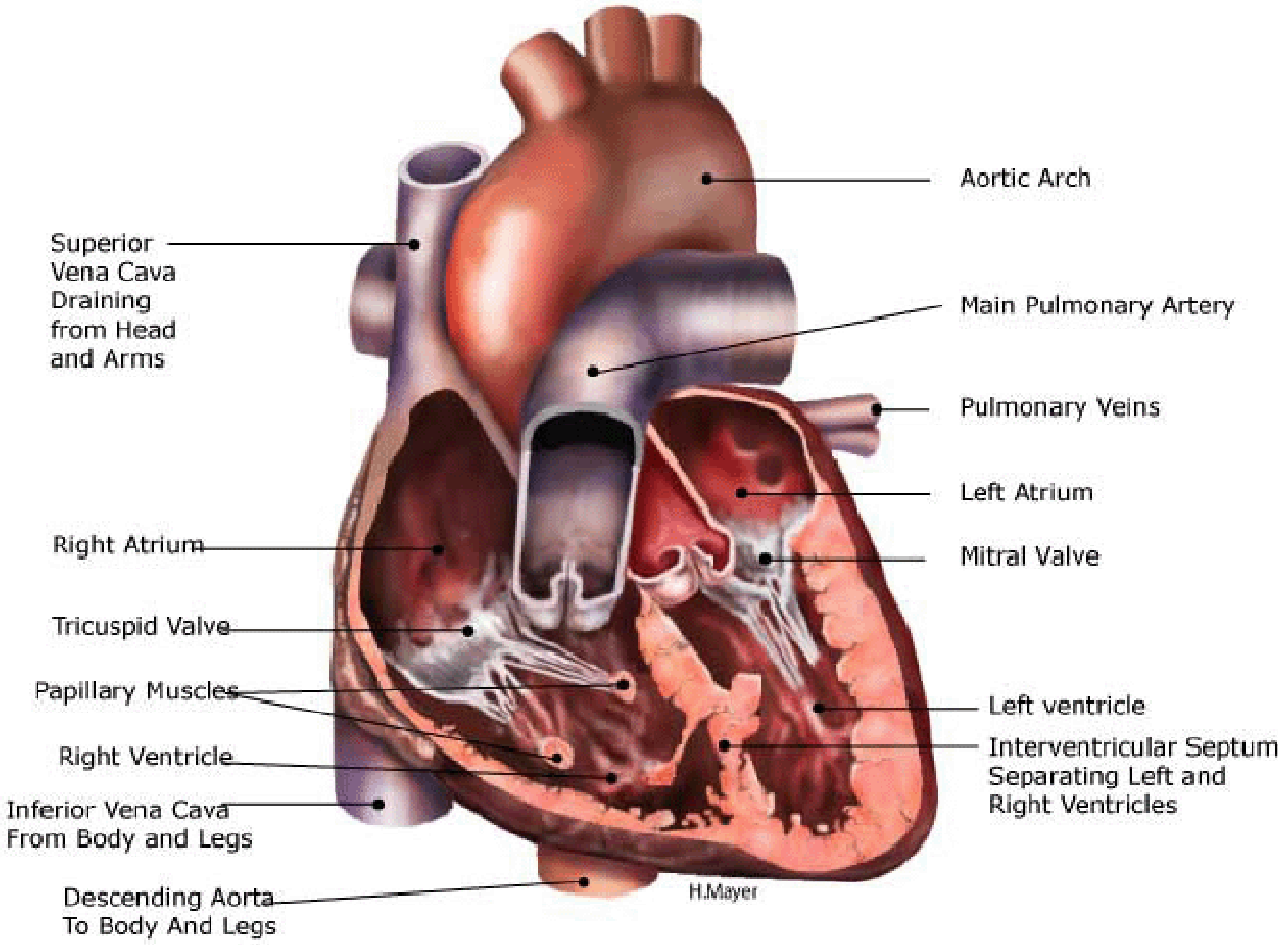
Investigation

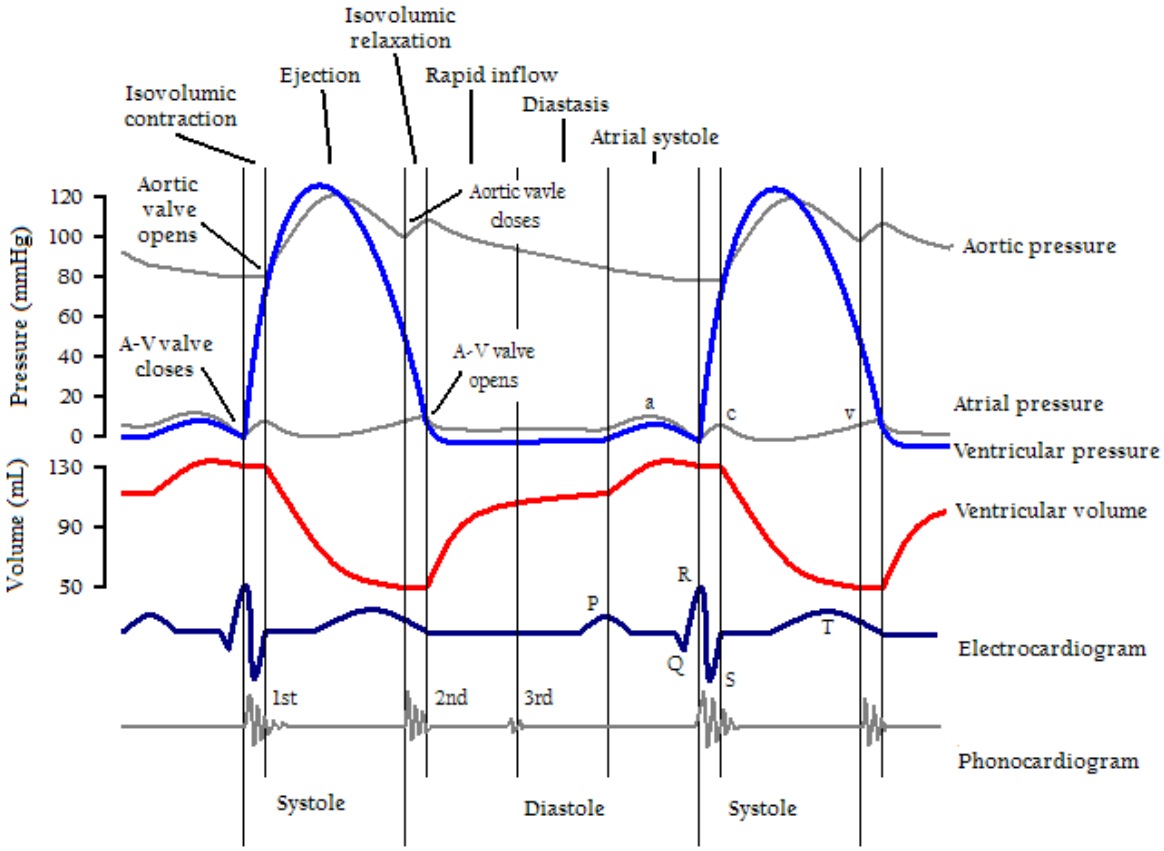
- Rheumatoid factor (RF) positive in nearly 100% of patients
- ANA positive in 70%
- Anti-Ro (SSA) antibodies in 70% of patients with PSS
- Anti-La (SSB) antibodies in 30% of patients with PSS
- Schirmer's test: filter paper near conjunctival sac to measure tear formation
- Histology: focal lymphocytic infiltration → (marked ↑ risk of lymphoid malignancy)
- Also: hypergammaglobulinemia, low C4

Management

- Artificial saliva and tears
- Pilocarpine may stimulate saliva production

CARDIOLOGY


Aortic Arch
Superior Vena Cava Draining from Head and Arms
Main Pulmonary Artery
Pulmonary Veins
Left Atrium
Right Atrium
Mitral Valve
Tricuspid Valve
Papillary Muscles
Left ventricle
Right Ventricle
Interventricular Septum Separating Left and Right Ventricles
Inferior Vena Cava From Body and Legs
Descending Aorta To Body And Legs
H.Mayer



Pulses:

Pulsus parodoxus

- Greater than the normal (10 mmHg) fall in systolic blood pressure during inspiration → faint or absent pulse in inspiration
- Severe asthma, cardiac tamponade

Slow-rising/plateau

- Aortic stenosis

Collapsing

- Aortic regurgitation
- Patent ductus arteriosus
- Hyperkinetic (anemia, thyrotoxic, fever, exercise/pregnancy)

Pulsus alternans

- Regular alternation of the force of the arterial pulse
- Severe LVF

Bisferiens pulse

- 'Double pulse' - two systolic peaks
- Mixed aortic valve disease

'Jerky' pulse

- Hypertrophic obstructive cardiomyopathy*

*HOCM may occasionally be associated with a bisferiens pulse

Heart Sounds: The first heart sound (S1) is caused by closure of the mitral and tricuspid valves whilst the second heart sound (S2) is due to aortic and pulmonary valve closure

Heart Sound	Characteristics
S1	• Closure of mitral and tricuspid valves • Soft if long PR or mitral regurgitation • Loud in mitral stenosis • Variable intensity in complete heart block
S2	caused by the closure of the aortic valve (A2) closely followed by that of the pulmonary valve (P2) Causes of a loud S2 • Hypertension: systemic (loud A2) or pulmonary (loud P2) • Hyperdynamic states • Atrial septal defect without pulmonary hypertension Causes of a soft S2 • Aortic stenosis Causes of fixed split S2 • Atrial septal defect Causes of a widely split S2 • Deep inspiration • RBBB • Pulmonary stenosis • Severe mitral regurgitation Causes of a reversed (paradoxical) split S2 (P2 occurs before A2) • LBBB • Severe aortic stenosis • Right ventricular pacing • WPW type B (causes early P2) • Patent ductus arteriosus
S3	• Caused by diastolic filling of the ventricle • Considered normal if < 30 years old (may persist in women up to 50 years old) • Heard in left ventricular failure, constrictive pericarditis • Gallop rhythm (S3) is an early sign of LVF
S4	• may be heard in aortic stenosis, HOCM, hypertension • caused by atrial contraction against a stiff ventricle • in HOCM a double apical impulse may be felt as a result of a palpable S4

Jugular Venous Pulse: as well as providing information on right atrial pressure, the jugular vein waveform may provide clues to underlying valvular disease. A non-pulsatile JVP is seen in superior vena caval obstruction. Kussmaul's sign describes a paradoxical rise in JVP during inspiration seen in constrictive pericarditis. **Kuss**maul's sign → **cons**trictive pericarditis

Wave	Characteristics
'a' wave	'a' wave = atrial contraction • Large if atrial pressure e.g. Tricuspid stenosis, pulmonary stenosis, pulmonary hypertension • Absent if in atrial fibrillation Cannon 'a' waves • Caused by atrial contractions against a closed tricuspid valve • Are seen in complete heart block, ventricular tachycardia/ectopics, nodal rhythm, single chamber ventricular pacing Cannon waves: May be subdivided into regular or intermittent Regular cannon waves • Ventricular tachycardia (with 1:1 ventricular-atrial conduction) • Atrio-ventricular nodal re-entry tachycardia (AVNRT) Irregular cannon waves • Complete heart block
'c' wave	• Closure of tricuspid valve • Not normally visible
'v' wave	• Giant v waves in tricuspid regurgitation
'x' descent	Fall in atrial pressure during ventricular systole
'y' descent	Opening of tricuspid valve

Cardiac Physiological changes during exercise:

Blood pressure

- Systolic ↑, diastolic ↓
- Leads to ↑ pulse pressure
- In healthy young people the ↑ in MABP is only slight

Cardiac output

- ↑ in cardiac output may be 3-5 fold
- Results from venous constriction, vasodilation and ↑ myocardial contractibility, as well as from the maintenance of right atrial pressure by an ↑ in venous return
- Heart rate up to 3-fold ↑
- Stroke volume up to 1.5-fold ↑

Left ventricular ejection fraction = (stroke volume / end diastolic LV volume) * 100%

Stroke volume = end diastolic LV volume - end systolic LV volume

ECG normal variants:

LBBB is always pathological

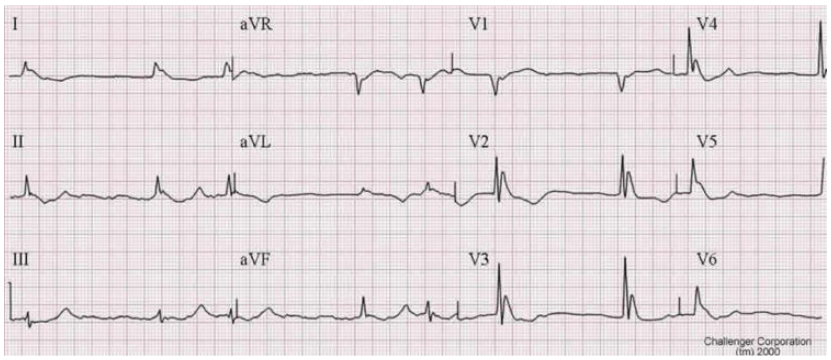
In an athlete:

- Sinus bradycardia
- Junctional rhythm
- First degree heart block
- Wenckebach phenomenon

ECG changes may be seen in hypothermia:

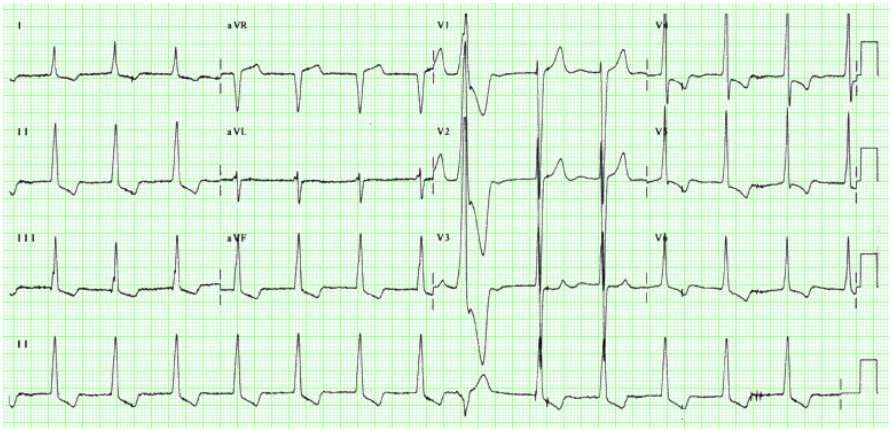
- Bradycardia
- 'J' wave - small hump at the end of the QRS complex
- First degree heart block
- Long QT interval
- Atrial and ventricular arrhythmias

J waves are seen in hypothermia whilst delta waves are associated with WPW



Digoxin ECG features:

- Down-sloping ST depression ('reverse tick')
- Flattened/inverted T waves
- Short QT interval
- Arrhythmias e.g. AV block, bradycardia



Causes of ST depression:

- Normal if upward sloping
- Ischemia
- Digoxin
- Hypokalemia
- Syndrome X

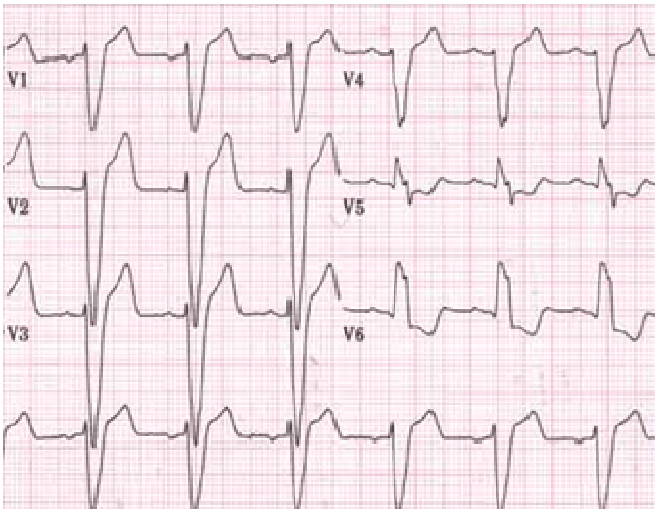
LBBB

Diagnosis: criteria to diagnose a left bundle branch block on ECG:

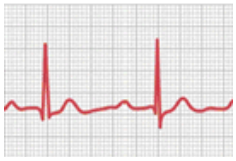
- Rhythm must be supraventricular in origin (P wave present)
- QRS duration ≥ 120 ms (3 small squares)
- QS or rS complex in lead V1(note: r is small-not capital = small-not tall r in ECG)
- RsR wave in lead V6.

Causes:

- Ischemic heart disease
- Hypertension
- Cardiomyopathy
- Idiopathic fibrosis



Prolonged PR interval



PR interval is lengthened beyond 0.20 seconds (>5small squares)
Also named: 1st degree heart block

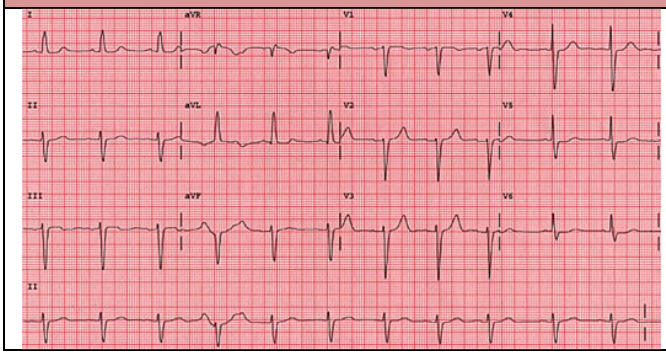
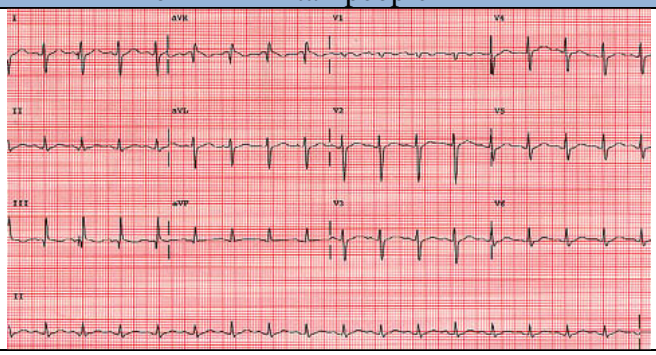
Causes:

- Idiopathic
- Ischemic heart disease
- Digoxin toxicity
- Hypokalemia*
- Rheumatic fever
- Aortic root pathology e.g. Abscess secondary to endocarditis
- Lyme disease
- Sarcoidosis
- Myotonic dystrophy

A prolonged PR interval may also be seen in athletes

*Hyperkalemia can rarely cause a prolonged PR interval.

Axis Deviation

Causes of left axis deviation (LAD)	Causes of right axis deviation (RAD)
• Left anterior hemiblock • Left bundle branch block • Wolff-parkinson-white syndrome* - right-sided accessory pathway • Hyperkalemia • Congenital: ostium **PRIMUM** ASD, tricuspid atresia • Minor LAD in obese people	• Right ventricular hypertrophy • Left posterior hemiblock • Chronic lung disease • Pulmonary embolism • Ostium **SECUNDUM** ASD • Wolff-parkinson-white syndrome* - left-sided accessory pathway • Normal in infant < 1 years old • Minor RAD in tall people
	

***in the majority of cases, or in a question without specification, Wolff-Parkinson-White syndrome is associated with left axis deviation**

Isolated systolic hypertension (ISH) is common in the elderly, affecting around 10% of people older than 70 years old. The Systolic Hypertension in the Elderly Program (SHEP) back in 1991 established that treating ISH ↓ both strokes and ischemic heart disease. Drugs such **as thiazides were recommended as first line agents**. This approach is not contraindicated by the 2006 NICE guidelines which recommend treating ISH in the **same** stepwise fashion **as standard hypertension**

Hypertension:

Initial drug choice

- Patients < 55-years-old: ACE inhibitor
- Patients > 55-years-old or of Afro-Caribbean origin: calcium channel blocker or thiazide diuretic

The target blood pressure is 140/90 mmHg

When diagnosis of HTN is unclear, ambulatory 24H BP monitor may be helpful

If this fails to control the blood pressure then use a combination of an ACE inhibitor plus either a calcium channel blocker or thiazide diuretic

If this still fails then a combination of an ACE inhibitor + calcium channel blocker + thiazide diuretic should be used

β-blockers are less likely to prevent stroke + potential impairment of glucose tolerance; this was demonstrated in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)

Causes of secondary HTN

- Renal - accounts for 80% of secondary hypertension
    - Glomerulonephritis
    - Pyelonephritis
    - Adult polycystic kidney disease
    - Renal artery stenosis

- Endocrine disorders
    - Cushing's syndrome
    - Primary hyperaldosteronism including Conn's syndrome
    - Liddle's syndrome
    - Congenital adrenal hyperplasia (11-β hydroxylase deficiency)
    - Pheochromocytoma
    - Acromegaly

- Others
    - Pregnancy
    - Coarctation of the aorta
    - The combined oral contraceptive pill
    - Steroids
    - Maoi

New drugs

Direct renin inhibitors

- e.g. Aliskiren (branded as Rasilez)
- By inhibiting renin blocks the conversion of angiotensinogen to angiotensin I
- No trials have looked at mortality data yet. Trials have only investigated fall in blood pressure. Initial trials suggest aliskiren ↓ blood pressure to a similar extent as angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists
- Adverse effects were uncommon in trials although diarrhea was occasionally seen
- Only current role would seem to be in patients who are intolerant of more established antihypertensive drugs

Examples of centrally acting antihypertensives include:

- Methyldopa: used in the management of hypertension during pregnancy
- Moxonidine: used in the management of essential hypertension when conventional antihypertensives have failed to control blood pressure
- Clonidine: the antihypertensive effect is mediated through stimulating α-2 adrenoceptors in the vasomotor center.

Hypertension and DM is an added cardiovascular risk factor for diabetics and should therefore by actively looked for and treated. It is also a risk factor for the development of diabetic nephropathy.

Selected points

- The blood pressure target for diabetics is 140/80 mmHg. If there is end-organ damage the target is 130/80 mmHg
- ACE inhibitors are first-line*. Otherwise managed according to standard NICE hypertension guidelines
- BNF advises to avoid the routine use of beta-blockers in uncomplicated hypertension,

particularly when given in combination with thiazides, as they may cause insulin resistance, impair insulin secretion and alter the autonomic response to hypoglycemia

*increase insulin sensitivity and can therefore theoretically cause hypoglycemia - rarely clinically relevant

Pericarditis:

Features

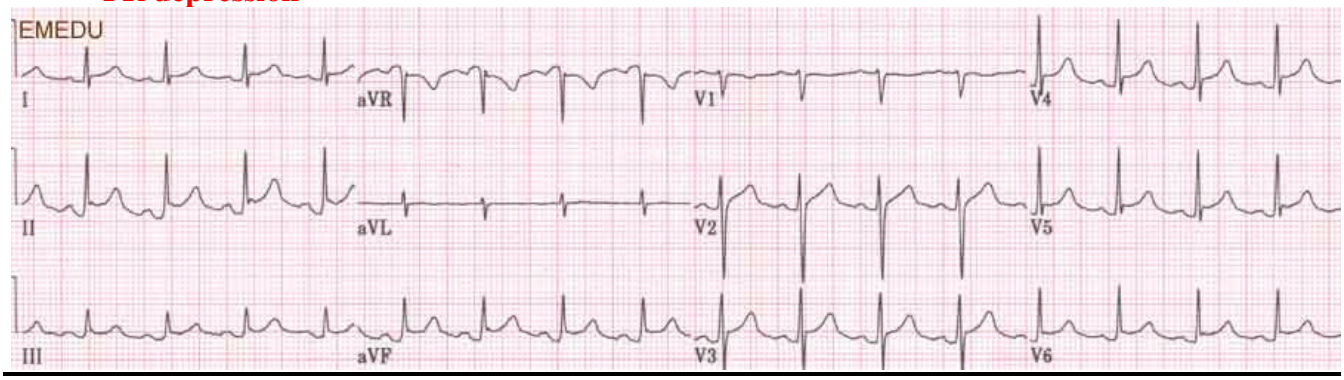
- Chest pain: may be pleuritic. Is often relieved by sitting forwards
- Other symptoms include non-productive cough, dyspnea and flu-like symptoms
- Pericardial rub
- Tachypnea
- Tachycardia

Causes

- Viral infections (Coxsackie)
- TB
- Uremia (causes 'fibrinous' pericarditis)
- Trauma
- Post MI, Dressler's syndrome
- Connective tissue disease
- Hypothyroidism

ECG changes

- Widespread 'saddle-shaped' ST elevation
- **PR depression**



Myocarditis:

Causes

- Viral: coxsackie, HIV
- Bacteria: diphtheria, clostridia
- Spirochetes: Lyme disease
- Protozoa: Chagas' disease, toxoplasmosis
- Autoimmune
- Drugs

Presentation

- Usually young patient with acute history
- Chest pain, SOB

Infective endocarditis: the **strongest risk factor for developing infective endocarditis is a previous episode of endocarditis**. Other factors include:

- Previously normal valves (50%, typically acute presentation)
- Rheumatic valve disease (30%)
- Prosthetic valves
- Congenital heart defects
- Intravenous drug users (IVDUS, e.g. Typically causing tricuspid lesion)

Most common cause of endocarditis:
- Streptococcus viridans
- Staphylococcus epidermidis if < 2 months post valve surgery

Causes

- *Streptococcus viridans* (most common cause - 40-50%) → has good prognosis
- *Staphylococcus epidermidis* (especially prosthetic valves)
- *Staphylococcus aureus* (especially acute presentation, IVDUS)
- *Streptococcus bovis* is associated with colorectal cancer
- *Bacteroides fragilis* endocarditis is very rare complication of colonic resection, bacteria reaches heart via venous return, this is why it affects right > left side → Treat with Metronidazole
- Non-infective: systemic lupus erythematosus (Libman-Sacks), malignancy: marantic endocarditis

Culture negative causes (BP-CHB)

- Brucella
- Prior antibiotic therapy
- *Coxiella burnetii*
- HACEK: Hemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella)
- Bartonella

Following prosthetic valve surgery *Staphylococcus epidermidis* is the most common organism in the first 2 months and is usually the result of perioperative contamination. After 2 months the spectrum of organisms which cause endocarditis return to normal, except with a slight ↑ in Staph aureus infections

Poor prognostic factors

- *Staph aureus* infection (see below)
- Prosthetic valve (especially 'early', acquired during surgery)
- Culture negative endocarditis
- Low complement levels

Mortality according to organism

- Staphylococci - 30%
- Bowel organisms - 15%
- Streptococci - 5%

Diagnosis

- Pathological criteria positive, or
- 2 major criteria, or
- 1 major and 3 minor criteria, or
- 5 minor criteria

Pathological criteria
Positive histology or microbiology of pathological material obtained at autopsy or cardiac surgery (valve tissue, vegetations, embolic fragments or intracardiac abscess content)
Major criteria
1. Positive blood cultures • Two positive blood cultures showing typical organisms consistent with infective endocarditis, such as *Streptococcus viridans* and the HACEK group. • Persistent bacteremia from two blood cultures taken > 12 hours apart or three or more positive blood cultures where the pathogen is less specific such as Staph aureus and Staph epidermidis. • Positive serology for *Coxiella burnetii*, Bartonella species or *Chlamydia psittaci*. • Positive molecular assays for specific gene targets
2. Evidence of endocardial involvement • Positive echocardiogram (oscillating structures, abscess formation, new valvular regurgitation or dehiscence of prosthetic valves), or • New valvular regurgitation
Minor criteria
• Predisposing heart disease • Microbiological evidence does not meet major criteria • Fever > 38ºc • Vascular phenomena: major emboli, splenomegaly, clubbing, splinter hemorrhages, petechiae or purpura • Immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots (boat shaped hemorrhages in retina) • Elevated CRP or ESR

Current management guidelines (source: British National Formulary)

- Initial **blind** therapy - **flucloxacillin + gentamicin** (benzylpenicillin + gentamicin if symptoms less severe)
- Initial **blind** therapy if **prosthetic** valve is present or patient is penicillin allergic - **vancomycin + rifampicin + gentamicin**
- Endocarditis caused by **staphylococci - flucloxacillin** (vancomycin + rifampicin if penicillin allergic or MRSA)
- Endocarditis caused by **streptococci → benzylpenicillin + gentamicin** (vancomycin + gentamicin if penicillin allergic)

Indications for surgery

- Severe valvular incompetence (both native and prosthetic)
- Early prosthetic valve endocarditis
- Aortic abscess (often indicated by a lengthening PR interval)
- Infections resistant to antibiotics/fungal infections
- Cardiac failure refractory to standard medical treatment
- Recurrent emboli after antibiotic therapy

- HACK group, brucella, coxilla, pseudo- aeruginosa and vancomycin resistant enterococci

The 2008 guidelines from NICE have radically changed the list of procedures for which antibiotic prophylaxis is recommended

NICE recommends the following procedures **do not require prophylaxis:**

- Dental procedures
- Upper and lower gastrointestinal tract procedures
- Genitourinary tract; this includes urological, gynecological and obstetric procedures and childbirth
- Upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy

The guidelines do however suggest:

- Any episodes of infection in people at risk of infective endocarditis should be investigated and treated promptly to ↓ the risk of endocarditis developing
- If a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary procedure at a site where there is a suspected infection they should be given an antibiotic that covers organisms that cause infective endocarditis

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Heart Failure: number of drugs have been shown to improve mortality in patients with chronic heart failure:

- ACE inhibitors (SAVE, SOLVD, CONSENSUS)
- Spironolactone (RALES)
- β-blockers (CIBIS)
- Hydralazine with nitrates (VHEFT-1)

Whilst spironolactone has been shown to improve prognosis in patients with chronic heart failure, no long-term reduction in mortality has been demonstrated for loop diuretics such as furosemide. NICE guidelines recommend the introduction of an ACE inhibitor prior to a β-blocker in patients with chronic heart failure.

NICE produced guidelines on management in 2003, key points include:

- All patients should be given an ACE inhibitor unless contradictions exist
- Once an ACE inhibitor has been introduced a β-blocker should be started regardless of whether the patient is still symptomatic
- Offer annual influenza vaccine
- Offer pneumococcal vaccine

Digoxin has also not been proven to ↓ mortality in patients with heart failure. It may however improve symptoms due to its inotropic properties. Digoxin is strongly indicated if there is coexistent atrial fibrillation

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(NYHA) The New York Heart Association (NYHA) classification is widely used to classify the severity of heart failure:

NYHA Class I

- No symptoms
- No limitation: ordinary physical exercise does not cause undue fatigue, dyspnea or palpitations

NYHA Class II

- Mild symptoms
- Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations or dyspnea

NYHA Class III

- Moderate symptoms
- Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms

NYHA Class IV

- Severe symptoms
- Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with ↑ discomfort with any physical activity

Pulmonary Edema:

American Heart Association Advanced Cardiac Life Support guidelines for the treatment of acute pulmonary edema is the same for all patients after initial evaluation:

- High-flow oxygen
- Furosemide 0.5-1 mg/kg IV
- Morphine 2-4 mg IV
- Sublingual nitroglycerine (GTN).
- Steps then are dictated by the systolic BP after initial treatment:
    - If the BP is >100 mmHg, start IV nitroglycerine 10-20 µg/min
    - BP of 70-100 mmHg, with no shock start IV dobutamine 2-20 µg/min
    - If the BP is 70-100 mmHg with shock, start IV dopamine 5-15 µg/min
    - If the BP is < 70 mmHg with shock, start IV noradrenaline 0.5-30 µg/min.

Further diagnostic and therapeutic considerations include investigation for myocardial ischemia or other underlying causes, and treatment with pulmonary artery catheter or intra-aortic balloon pump.

Diastolic Heart Failure:

Basics:

- 1/3 of heart failure is diastolic (normal Left Ventricular Systolic Function-LVSF)
- Mortality in Diastolic HF is 5-8% (lower than Systolic HF: 10-15%)

Diagnosis:

- Echo is the golden diagnostic tool
- CXR and ECG cannot differentiate Diastolic vs. Systolic HF.

Management:

- Initially, reduction of pulmonary venous pressure (PVP) and congestion, using diuretics
- ARBs are superior to ACE inhibitors

Cardiac Tamponade:

Features

- Raised JVP, with an absent Y descent - this is due to the limited right ventricular filling
- Tachycardia
- Hypotension
- Muffled heart sounds
- Pulsus paradoxus (which occurs also in Asthma)
- Kussmaul's sign (much debate about this) (more in constrictive pericarditis)
- ECG: electrical alternans

The key differences between constrictive pericarditis and cardiac tamponade are summarized below:

	Cardiac tamponade	Constrictive pericarditis
JVP	Absent Y descent	X + Y present
Pulsus paradoxus	Present	Absent
Kussmaul's sign	Rare	Present
Characteristic features		Pericardial calcification on CXR

A commonly used mnemonic to remember the absent Y descent in cardiac tamponade is TAMponade = TAMpaX

DVLA - Cardiology

The April 2009 AKT feedback report made specific mention of fitness to drive rules. The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Specific rules

- Angioplasty (elective) - 1 week off driving
- CABG - 4 weeks off driving
- Acute coronary syndrome- 4 weeks off driving, 1 week if successfully treated by angioplasty
- Angina - driving must cease if symptoms occur at rest/at the wheel
- Pacemaker insertion - 1 week off driving
- Implantable cardioverter-defibrillator: if implanted for sustained ventricular arrhythmia: cease driving for 6 months. If implanted prophylatically then cease driving for 1 month
- Successful catheter ablation - 2 days off driving
- Aortic aneurysm > 6cm - notify DVLA. Licensing will be permitted subject to annual review. An aortic diameter of 6.5 cm or more disqualifies patients from driving
- Heart transplant: DVLA do not need to be notified

Cardiac Imaging & Investigations:

The ability to image the heart using non-invasive techniques such as MRI, CT and radionuclides has evolved rapidly over recent years.

Nuclear imaging: These techniques use radiotracers which are extracted by normal myocardium. Examples include:

- Thallium
- 'MIBI' or (SPECT) scans: Cardiac Single Photon Emission Computed Tomography uses Technetium (99mTc) sestamibi, a coordination complex of the radioisotope technetium-99m with the ligand methoxyisobutylisonitrile (MIBI).

- Positron Emission Tomography (PET) scans: Fluordeoxyglucose (FDG) is used.

The primary role of SPECT is to assess myocardial perfusion and myocardial viability. Two sets of images are usually acquired. First the myocardium at rest followed by images of the myocardium during stress (either exercise or following adenosine / dipyridamole). By comparing the rest with stress images any areas of ischemia can be classified as reversible or fixed (e.g. following a myocardial infarction). Cardiac PET is predominately a research tool at the current time

MUGA

- Multi Gated Acquisition Scan, also known as radionuclide angiography
- Radionuclide (technetium-99m) is injected intravenously
- The patient is placed under a gamma camera
- May be performed as a stress test
- Can accurately measure left ventricular ejection fraction. Typically used before and after cardiotoxic drugs are used

Cardiac Computed Tomography (CT): useful for assessing suspected IHD, using two main methods:

- Calcium score: there is known to be a correlation between the amount of atherosclerotic plaque calcium and the risk of future ischemic events. Cardiac CT can quantify the amount of calcium producing a 'calcium score'
- Contrast enhanced CT: allows visualization of the coronary artery lumen

If these two techniques are combined cardiac CT has a very high negative predictive value for ischemic heart disease.

Cardiac MRI: (commonly termed CMR) has become the gold standard for providing structural images of the heart. It is particularly useful when assessing **congenital heart disease**, determining right and left ventricular mass and differentiating forms of **cardiomyopathy**. Myocardial perfusion can also be assessed following the administration of gadolinium. Currently CMR provides limited data on the extent of coronary artery disease.

Exercise ECG:
USELESS in patients with:

- Conduction abnormalities
- resting (ECG) abnormalities like ST segment depression of >1mm
- WPW
- Digoxin
- Ventricular paced rhythm

In such patients myocardial perfusion imaging is the preferred modality for evaluation of CAD.

CORONARY ARTERY DISEASES

Chest Pain: NICE issued guidelines in 2010 on the 'Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin'.

Patients presenting with acute chest pain

Immediate management of suspected acute coronary syndrome (ACS)

- Glyceryl trinitrate
- Aspirin 300mg. NICE do not recommend giving other antiplatelet agents (i.e. Clopidogrel) outside of hospital
- Do not routinely give oxygen, only give if sats < 94%*
- Perform an ECG as soon as possible but do not delay transfer to hospital. A normal ECG does not exclude ACS

Referral

- Current chest pain or chest pain in the last 12 hours with an abnormal ECG: emergency admission
- Chest pain 12-72 hours ago: refer to hospital the same-day for assessment
- Chest pain > 72 hours ago: perform full assessment with ECG and troponin measurement before deciding upon further action

NICE suggest the following in terms of oxygen therapy:

- Do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:
- People with oxygen saturation (SpO2) < 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO2 of 94-98%
- People with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO2 of 88-92% until blood gas analysis is available.

Patients presenting with stable chest pain

With all due respect to NICE the guidelines for assessment of patients with stable chest pain are rather complicated. They suggest an approach where the risk of a patient having coronary artery disease (CAD) is calculated based on their symptoms (whether they have typical angina, atypical angina or non-anginal chest pain), age, gender and risk factors.

NICE define anginal pain as the following:

  - Constricting discomfort in the front of the chest, neck, shoulders, jaw or arms
  - Precipitated by physical exertion
  - Relieved by rest or GTN in about 5 minutes

- Patients with all 3 features have typical angina
- Patients with 2 of the above features have atypical angina
- Patients with 1 or none of the above features have non-anginal chest pain

If patients have typical anginal symptoms and a risk of CAD is greater than 90% then no further diagnostic testing is required. It should be noted that all men over the age of 70 years who have typical anginal symptoms fall into this category.

For patients with an estimated risk of 10-90% the following investigations are recommended. Note the absence of the exercise tolerance test:

Risk	Diagnostic testing
61-90%	Coronary angiography
30-60%	Functional imaging, for example: • Myocardial perfusion scan with SPECT • Stress echocardiography • First-pass contrast-enhanced magnetic resonance (MR) perfusion • MR imaging for stress-induced wall motion abnormalities.
10-29%	CT calcium scoring

Stable Angina: the management of stable angina comprises lifestyle changes, medication, percutaneous coronary intervention and surgery.

NICE 2011 Guidelines:
- In good exercise tolerance, consider medical therapy before angiography (β-blocker is the most important)
- If pain is worsening, no need for exercise test, directly do angiography (Cath)

Medication
- All patients should receive aspirin and a statin in the absence of any contraindication
- Sublingual glyceryl trinitrate to abort angina attacks
- β-blocker is the preferred initial treatment. For patients unable to take a β-blocker there is no clear guidelines on the best alternative. Options include a rate-limiting calcium-channel blocker (verapamil or diltiazem); a long-acting dihydropyridine calcium-channel blocker (e.g. modified-release nifedipine); a nitrate; or a potassium-channel activator
- If there is a poor response to initial treatment then the β-blocker should be ↑ to the maximum tolerated dose (e.g. atenolol 100mg od)
- Again, there are no clear guidelines on the next step treatment. CKS advise adding a long-acting dihydropyridine (e.g. nifedipine, amlodepine, felodipine) although other options include isosorbide mononitrate and nicorandil

Prinzmetal angina - treatment = dihydropyridine calcium channel blocker (depine family; amlodepine)

Nitrate tolerance
- Many patients who take nitrates develop tolerance and experience ↓ efficacy
- BNF advises that patients who develop tolerance should take the second dose of isosorbide mononitrate after 8 hours, rather than after 12 hours. This allows blood-nitrate levels to fall for 4 hours and maintains effectiveness
- This effect is not seen in patients who take modified release isosorbide mononitrate

Ivabradine (Procoralan)
- A new class of anti-anginal drug which works by reducing the heart rate
- Acts on the I_f ('funny') ion current which is highly expressed in the sinoatrial node, reducing cardiac pacemaker activity
- Adverse effects: visual effects, particular luminous phenomena, are common. Bradycardia, due to the mechanism of action, may also be seen
- There is no evidence currently of superiority over existing treatments of stable angina

Acute Coronary Syndrome: The management of non-ST elevation acute coronary syndrome is based upon the calculation of a risk score, for example TIMI (Thrombolysis In Myocardial Infarction)

All patients should receive
- Aspirin 300mg
- Nitrates or morphine to relieve chest pain if required

Clopidogrel 300mg and low molecular weight heparin (principally enoxaparin) should also be added to higher risk patients

Whilst it is common that non-hypoxic patients receive oxygen therapy there is little evidence to support this approach. The 2008 British Thoracic Society oxygen therapy guidelines advise **NOT GIVING OXYGEN UNLESS THE PATIENT IS HYPOXIC**.

Antithrombin treatment. Fondaparinux should be offered to patients who are not at a high risk of bleeding and who are not having angiography within the next 24 hours. If angiography is likely within 24 hours or a patient's creatinine is > 265 µmol/l unfractionated heparin should be given.

Clopidogrel 300mg should be given to patients with a predicted 6 month mortality of more than 1.5% or patients who may undergo percutaneous coronary intervention within 24 hours of admission to hospital. Clopidogrel should be continued for 12 months.

Clopidogrel (Plavix®) Interactions
- Concurrent use of proton pump inhibitors (PPIs) may make clopidogrel less effective (MHRA July 2009)
- This advice was updated by the MHRA in April 2010, evidence seems inconsistent but omeprazole and esomeprazole still cause for concern. Other PPIs such as lansoprazole should be OK

Intravenous **glycoprotein IIb/IIIa receptor antagonists** (eptifibatide or tirofiban) should be given to patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%), and who are scheduled to undergo angiography within 96 hours of hospital admission.

Coronary angiography should be considered within 96 hours of first admission to hospital to patients who have a predicted 6-month mortality above 3.0%. It should also be performed as soon as possible in patients who are clinically unstable.

The table below summaries the mechanism of action of drugs commonly used in the management of acute coronary syndrome:

Aspirin	Antiplatelet - inhibits the production of thromboxane A2
Clopidogrel	Antiplatelet - inhibits ADP binding to its platelet receptor
Enoxaparin	Activates antithrombin III, which in turn potentiates the inhibition of coagulation factors Xa
Fondaparinux	Activates antithrombin III, which in turn potentiates the inhibition of coagulation factors Xa
Bivalirudin	Reversible direct thrombin inhibitor

Poor prognostic factors:

- Age
- Development (or history) of heart failure, Killip class*
- Peripheral vascular disease
- ↓ systolic blood pressure
- Initial serum creatinine concentration
- Elevated initial cardiac markers
- Cardiac arrest on admission
- ST segment deviation

***Killip class** - system used to stratify risk post myocardial infarction

Killip class	Features	30 day mortality
I	No clinical signs heart failure	6%
II	Lung crackles, S3	17%
III	Frank pulmonary edema	38%
IV	Cardiogenic shock	81%

Myocardial Infarction (MI):

Coronary Circulation (arterial supply of the heart)

- Posterior aortic or coronary sinus → left coronary artery (LCA)
- Anterior aortic or coronary sinus → right coronary artery (RCA)
- LCA (Left Main, LM) → LAD + circumflex
- RCA → posterior descending
- RCA supplies SA node in 60%, AV node in 90%

Venous drainage of the heart: coronary sinus drains into the right atrium

	ECG changes	Coronary artery
Anteroseptal	V1-V4	Left anterior descending
Inferior	II, III, aVF	Right coronary
Anterolateral	V4-6, I, aVL	Left anterior descending or left circumflex
Lateral	I, aVL +/- V5-6	Left circumflex
Posterior	Tall R waves V1-2	Usually left circumflex, also right coronary

All patients should be offered the following drugs:

- ACE inhibitor
- β-blocker
- Aspirin
- Statin

Clopidogrel

- After an ST-segment-elevation MI, patients treated with a combination of aspirin and clopidogrel during the first 24 hours after the MI should continue this treatment for at least 4 wk
- (NSTEMI): following the 2010 NICE unstable angina and NSTEMI guidelines clopidogrel should be given for the first 12 months if the 6 month mortality risk is > 1.5%
- Improves prognosis post MI
- Side effect: < 1% TTP usually 2 weeks after commencing the drug.

Aldosterone antagonists

- Patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-

MI treatment should be initiated within 3-14 days of the MI, preferably after ACE inhibitor therapy

Contraindications to Thrombolysis

- Active internal bleeding
- Recent hemorrhage, trauma or surgery (including dental extraction)
- Coagulation and bleeding disorders
- Intracranial neoplasm
- Stroke < 2 months
- Aortic dissection
- Recent head injury
- Pregnancy
- Severe hypertension

Dressler's Syndrome: This usually occurs 1 to 8 weeks after MI.

Presentation:

- Malaise, fever, pericardial pain
- Elevated erythrocyte count
- Sometimes may also have pleuritis and pneumonitis.

It has been postulated that the syndrome results from release of cardiac antigens which then stimulate antibody production. The immune complexes are then deposited in the pericardium, pleura and lung. There may be accompanying pleural and pericardial effusion and therefore echocardiography should be done.

Treatment involves aspirin and analgesics. Corticosteroids and non-steroidal anti-inflammatory agents are best avoided in the first 4 weeks after MI as they delay myocardial healing. Aspirin in large doses is effective. Recurrences can occur, and in such cases colchicine is helpful.

ST Elevation Myocardial Infarction (STEMI): a number of studies over the past 10 years have provided an evidence for the management of ST-elevation myocardial infarction (STEMI)

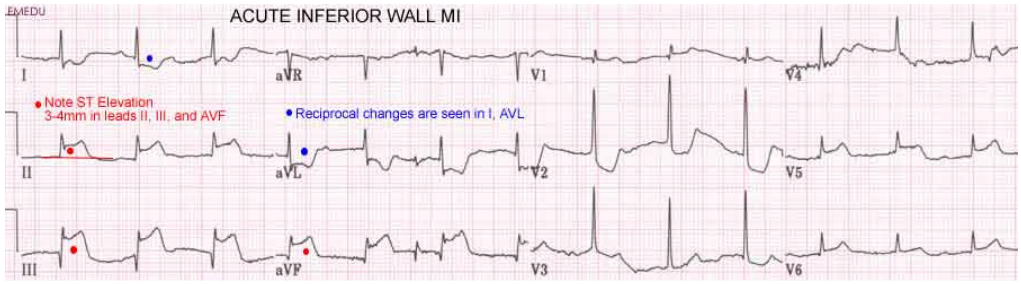
In the absence of contraindications, all patients should be given

- Aspirin
- Clopidogrel: the two major studies (clarity and commit) both confirmed benefit but used different loading doses (300mg and 75mg respectively)
- Low molecular weight heparin

Primary percutaneous coronary intervention (**PCI**) has emerged as **the gold-standard treatment** for STEMI but is not available in all centers. Thrombolysis should be performed in patients without access to primary PCI

With regards to thrombolysis:

- Tissue plasminogen activator (TPA) has been shown to offer clear mortality benefits over streptokinase
- Tenecteplase is easier to administer and has been shown to have non-inferior efficacy to alteplase with a similar adverse effect profile



- An ECG should be performed 90 minutes following thrombolysis to assess whether there has been a greater than 50% resolution in the ST elevation
- If there has not been adequate resolution then rescue PCI is superior to repeat thrombolysis
- For patients successfully treated with thrombolysis PCI has been shown to be beneficial. The optimal timing of this is still under investigation

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Percutaneous Coronary Intervention (PCI) is a technique used to restore myocardial perfusion in patients with ischemic heart disease, both in patients with stable angina and acute coronary syndromes. Stents are implanted in around 95% of patients - it is now rare for just balloon angioplasty to be performed. Before PCI, visualization of the coronaries is needed using diagnostic angiography.

Coronary Angiography (CAG) complications:

- Vascular complications: the most common complication overall is hemorrhage from access (right femoral artery mostly then right radial artery), much less common is rupture of coronary artery during revascularization or rupture of any artery from access to target artery
- Contrast Induced Nephropathy (CIN), higher incidence in diabetic patients and patients known to have renal dysfunction (prevented by good hydration)
- Cholesterol embolisation
- Arrhythmias (include arrest, ventricular and supraventricular) especially in primary intervention (in case of acute MI)
- Reaction to contrast

Following stent insertion migration and proliferation of smooth muscle cells and fibroblasts occur to the treated segment. The stent struts eventually become covered by endothelium. Until this happens there is ↑ risk of platelet aggregation leading to thrombosis.

Two main complications may occur due to stenting:

- Stent thrombosis: due to platelet aggregation as above. Occurs in 1-2% of patients, most commonly in the first month. Usually presents with acute myocardial infarction
- Restenosis: due to excessive tissue proliferation around stent. Occurs in around 5-20% of patients, most commonly in the first 3-6 months. Usually presents with the recurrence of angina symptoms. Risk factors include diabetes, renal impairment and stents in venous bypass grafts

Types of stent

- Bare-metal stent (BMS)
- Drug-eluting stents (DES): stent coated with paclitaxel or rapamycin which inhibit local tissue growth. Whilst this ↓ restenosis rates the stent thrombosis rates are ↑ as the process of stent endothelisation is slowed

BMS in T2DM: restenosis risk in 6 months is 40-50%

Following insertion the most important factor in preventing stent thrombosis is antiplatelet therapy. Aspirin should be continued indefinitely. The length of clopidogrel treatment depends on the type of stent, reason for insertion and consultant preference.

Clopidogrel is a pro-drug whose action may be related to adenosine diphosphate (ADP) receptor on platelet cell membranes. The specific subtype of ADP receptor that clopidogrel irreversibly inhibits is P2Y12 and is important in platelet aggregation and the cross-linking of platelets by fibrin. The blockade of this receptor inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway. The IIb/IIIa complex functions as a receptor mainly for fibrinogen and vitronectin but also for fibronectin and von Willebrand factor. Activation of this receptor complex is the "final common pathway" for platelet aggregation, and is important in the cross-linking of platelets by fibrin.

Platelet inhibition can be demonstrated two hours after a single dose of oral clopidogrel, but the onset of action is slow, so that a loading-dose of 300-600 mg is usually administered.

Cholestrol Embolism:

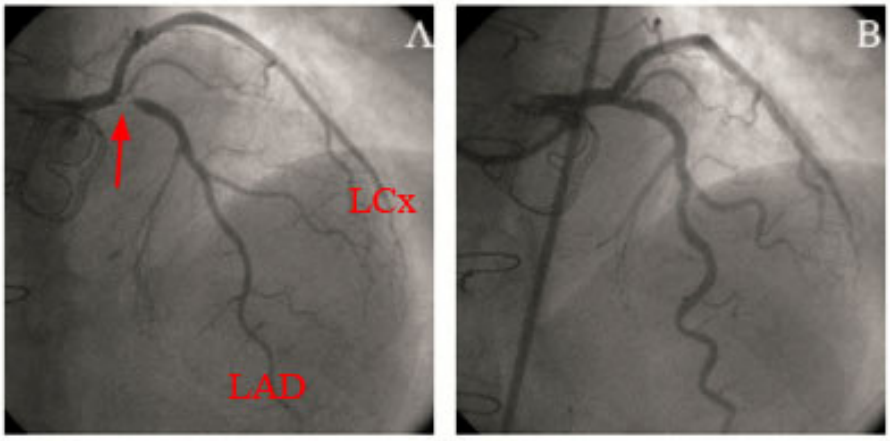
Cholesterol embolisation is a well-documented complication of coronary angiography

Overview

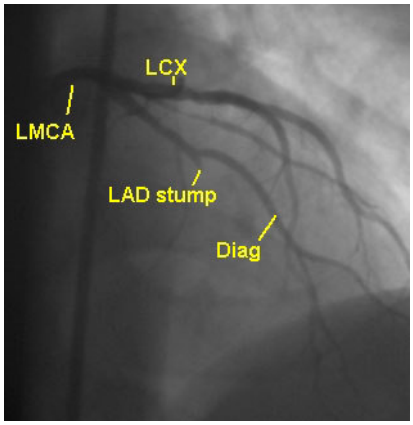
- Cholesterol emboli may break off causing renal disease
- Seen more commonly in arteriopaths, abdominal aortic aneurysms

Features

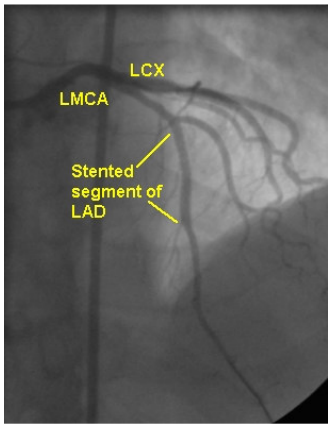
- Eosinophilia
- Purpura
- Renal failure
- Livedo reticularis (is a common cutaneous finding consisting of a mottled reticulated vascular pattern that appears like a lace-like purplish discoloration of the lower extremities, caused by swelling of (venules) in the skin, which makes them more visible)



(A) Subtotal occlusion of LAD [arrow] – (B) Post revascularization with stenting



Totally occluded LAD in anterior MI

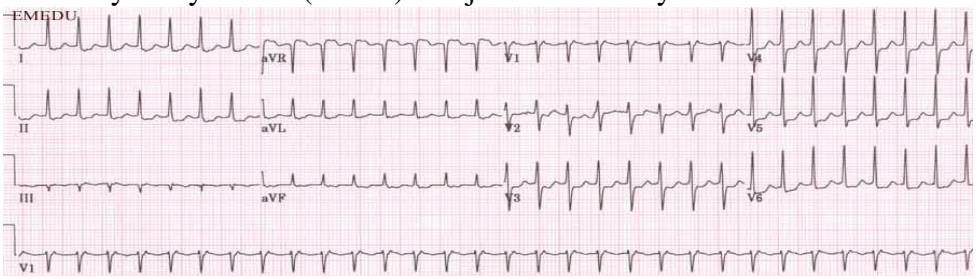


LAD after stenting, fully revascularized

LAD: Left Anterior Descending – LCx: Left Circumflex – LMCA: Left Main Coronary Artery – Diag: Diagonal branch of LAD

CARDIAC ARRHYTHMIA

Supraventricular tachycardia (SVT): Whilst strictly speaking the term supraventricular tachycardia (SVT) refers to any tachycardia that is not ventricular in origin the term is generally used in the context of paroxysmal SVT. Episodes are characterized by the sudden onset of a narrow complex tachycardia, typically an atrioventricular nodal re-entry tachycardia (AVNRT). Other causes include atrioventricular re-entry tachycardias (AVRT) and junctional tachycardias.



Acute management

- Vagal maneuvers: e.g. Valsalva maneuver
- Adenosine 6mg then 12mg then 12mg - contraindicated in asthmatics - verapamil is a preferable option (if no control) then
- Electrical cardioversion

Prevention of episodes

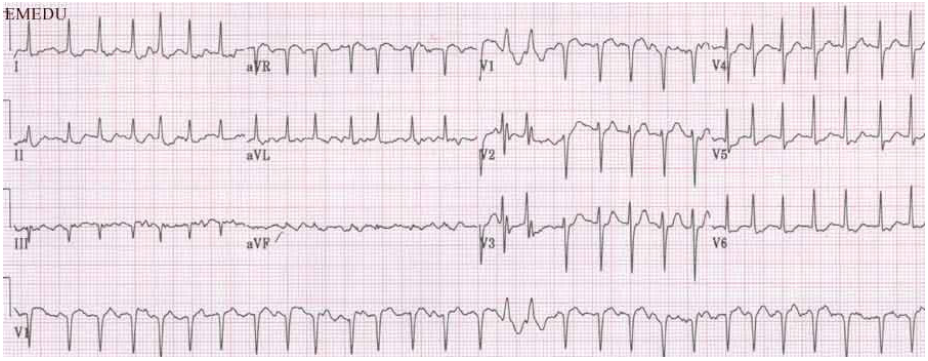
- β-blockers (Sotalal)
- Flecainide.
- Radio-frequency ablation

Premature Ventricular Contractions (PVCs): usually insignificant unless:

- Occurring frequently (≥6 beats/min)
- Bigeminal rhythm
- Short runs of ventricular tachycardia (V. Tach)
- R-on-T phenomenon
- Associated with serious organic heart disease
- Left ventricular decompensation (Decompensated Heart Failure)

Atrial fibrillation (AF): The Royal College of Physicians and NICE published guidelines on the management of atrial fibrillation (AF) in 2006. The following is also based on the joint American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) 2002 guidelines

Atrial fibrillation - cardioversion: amiodarone + flecainide



Agents with proven efficacy in the pharmacological cardioversion of atrial fibrillation

- Amiodarone
- Flecainide (if no structural heart disease)
- Others (less commonly used in UK): quinidine, dofetilide, ibutilide, propafenone

Less effective agents

- β-blockers (including sotalol)
- Calcium channel blockers
- Digoxin
- Disopyramide
- Procainamide

Onset < 48 hours

If atrial fibrillation (AF) is of less than 48 hours onset patients should be heparinised and a **transthoracic echocardiogram** performed to exclude a thrombus. Following this, patient may be cardioverted, either:

- Electrical - 'DC cardioversion'
- Pharmacology - amiodarone if structural heart disease, flecainide in those without structural heart disease

Following electrical cardioversion if AF is confirmed as being less than 48 hours duration then further anticoagulation is unnecessary

Onset > 48 hours

If AF is of greater than 48 hours then patients should have therapeutic anticoagulation for at least 3 weeks. If there is a high risk of cardioversion failure (e.g. previous failure or AF recurrence) then it is recommended to have at least 4 weeks amiodarone or sotalol prior to electrical cardioversion. If there was very acute history on presentation and the patient was in significant heart failure then DC cardioversion would be appropriate, as per Advanced Life Support guidelines.

Following electrical cardioversion patients should be anticoagulated for at least 4 weeks. After this time decisions about anticoagulation should be taken on an individual basis depending on the risk of recurrence.

Agents used to **control rate** in patients with atrial fibrillation

- β-blockers
- Calcium channel blockers
- Digoxin

Agents used to **maintain sinus rhythm** in patients with a history of atrial fibrillation

- Sotalol
- Amiodarone
- Flecainide
- Others (less commonly used in UK): disopyramide, dofetilide, procainamide, propafenone, quinidine

Factors favoring rate control	Factors favoring rhythm control
• Older than 65 years • History of ischemic heart disease	• Younger than 65 years • Symptomatic • First presentation • Lone AF or 2$^{nd°}$ AF (e.g. alcohol) • Congestive heart failure

An attempt was made in the joint American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) 2002 guidelines to simplify and clarify the classification of atrial fibrillation (AF).

It is recommended that AF be classified into 3 patterns:

- First detected episode (irrespective of whether it is symptomatic or self-terminating)
- Recurrent episodes, when a patient has 2 or more episodes of AF. If episodes of AF terminate spontaneously then the term **paroxysmal AF** is used (the most AF that benefit from β blocker). Such episodes last less than 7 days (typically < 24 hours). If the arrhythmia is not self-terminating then the term **persistent AF** is used. Such episodes usually last greater than 7 days
- In **permanent AF** there is continuous atrial fibrillation which cannot be cardioverted or if attempts to do so are deemed inappropriate. Treatment goals are therefore rate control and anticoagulation if appropriate

Supraventricular arrhythmias (including AF) secondary to acute alcohol intake are well characterized and have been termed 'holiday heart syndrome'. **No specific treatment is required**

Stroke Prophylaxis the guidelines suggest a stroke risk stratification approach when determining how to anticoagulate a patient, as detailed below:

The Royal College of Physicians and NICE published guidelines on the management of atrial fibrillation (AF) in 2006. But in practice these guidelines are usually alternated to the common **CHADS2** score:

	Condition	**Points**
C	Congestive heart failure	1
H	Hypertension (or treated hypertension)	1
A	Age > 75 years	1
D	Diabetes	1
S2	Prior Stroke or TIA	2

The table below shows a suggested anticoagulation strategy based on the score:

Score	**Anticoagulation**
0	Aspirin
1	Aspirin or warfarin, depending on patient preference and individual factors
2	Warfarin if not contraindicated

The Royal College of Physicians and NICE are due to publish joint guidelines on the management of atrial fibrillation (AF) in 2006:

Recommendations include:

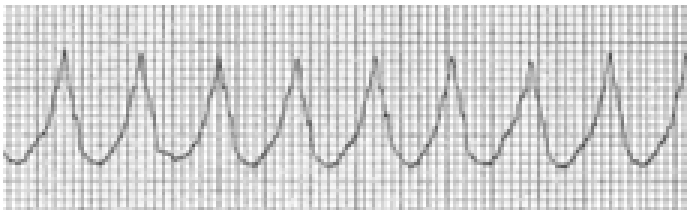
- Following a stroke or transient-ischemic attack (TIA) warfarin should be given as the anticoagulant of choice. Aspirin/dipyridamole should only be given if needed for the treatment of other comorbidities
- In acute stroke patients, in the absence of hemorrhage, anticoagulation therapy should be commenced after 2 weeks. If imaging shows a very large cerebral infarction then the initiation of anticoagulation should be delayed

Ventricular Tachycardia: Whilst a broad complex tachycardia may result from a supraventricular rhythm with aberrant conduction, the European Resuscitation Council advise that in a peri-arrest situation it is assumed to be ventricular in origin.

There are two main **types of VT**:

- Monomorphic VT: most commonly caused by myocardial infarction
- Polymorphic VT: A subtype of polymorphic VT is torsades de pointes which is precipitated by prolongation of the QT interval. The causes of a long QT interval are listed later.

If the patient has adverse signs (systolic BP < 90 mmHg, chest pain, heart failure or rate > 150 beats/min) then immediate cardioversion is indicated. In the absence of such signs antiarrhythmics may be used. If these fail, then electrical cardioversion may be needed with synchronised DC shocks



Features suggesting VT rather than SVT with aberrant conduction

- AV dissociation
- Fusion or capture beats
- Positive QRS concordance in chest leads
- Marked left axis deviation
- History of IHD
- Lack of response to adenosine or carotid sinus massage
- QRS > 160 ms

Drug therapy

- Amiodarone: ideally administered through a central line
- Lidocaine: use with caution in severe left ventricular impairment
- Procainamide

VERAPAMIL SHOULD NOT BE USED IN VT

Verapamil should never be given to a patient with a broad complex tachycardia as it may precipitate ventricular fibrillation in patients with ventricular tachycardia. Adenosine is sometimes given in this situation as a 'trial' if there is a strong suspicion the underlying rhythm is a supraventricular tachycardia with aberrant conduction

V Tach in Digoxin Toxicity:

- Treat with lidocaine and phenytoin
- Avoid Amiodarone and Procainamide (↑ Toxicity)
- D/C shock when all measures fail (but usually unsuccessful)

If drug therapy fails

- Electrophysiological study (EPS)
- Implant able cardioverter-defibrillator (ICD) - this is particularly indicated in patients with significantly impaired LV function

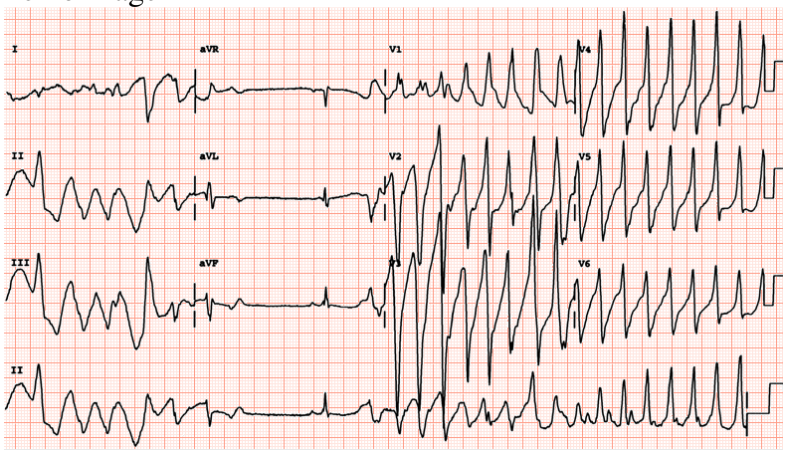
Torsades De Pointes ('twisting of the points') is a rare arrhythmia associated with a long QT interval. It may deteriorate into ventricular fibrillation and hence lead to sudden death

Risk factors:

- ♀
- ↓ HR
- CHF
- Digoxin
- Prolonged QT and Subclinical long QT syndrome
- Severe alkalosis
- Recent conversion from AF

Causes of long QT interval

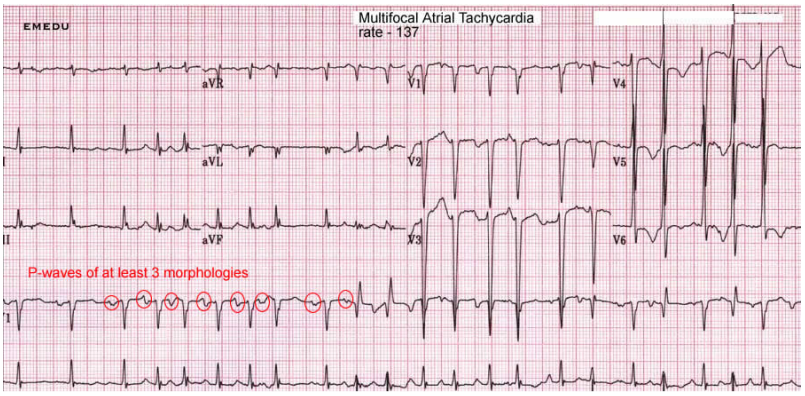
- Congenital: Jervell-Lange-Nielsen syndrome, Romano-Ward syndrome
- Antiarrhythmics: amiodarone, sotalol, class I-a antiarrhythmic drugs
- Tricyclic antidepressants
- Antipsychotics
- Chloroquine
- Terfenadine
- Erythromycin
- Electrolyte: **Hypocalcemia, Hypokalemia, Hypomagnesemia**
- Myocarditis
- **Hypothermia**
- Subarachnoid hemorrhage



Management

- IV magnesium sulphate
- Correct K^+ if hypo
- Override pacing (set pacemaker to be faster than patient rate then decrease the rate)
- D/C shock

Multifocal Atrial Tachycardia (MAT) may be defined as irregular cardiac rhythm caused by at least three different sites in the atria, which may be demonstrated by morphologically distinctive P waves. It is more common in elderly patients with chronic lung disease (e.g COPD)



Management

- Correction of hypoxia and electrolyte disturbances
- Rate-limiting calcium channel blockers are often used first-line
- **Cardioversion and digoxin are not useful in the management of MAT**

Tachycardia and Peri-Arrest: The joint European Resuscitation Council and Resuscitation Council (UK) 2005 guidelines have simplified the advice given for the management of peri-arrest tachycardias. Separate algorithms for the management of broad-complex tachycardia, narrow complex tachycardia and atrial fibrillation have been replaced by one unified treatment algorithm

Following basic ABC assessment, patients are classified as being stable or unstable according to the presence of any adverse signs:

- Systolic BP < 90 mmHg
- ↓ conscious level
- Chest pain
- Heart failure

If any of the above adverse signs are present then synchronised DC shocks should be given

Treatment following this is given according to whether the QRS complex is narrow or broad and whether the rhythm is regular or irregular. The full treatment algorithm can be found at the Resuscitation Council website, below is a very limited summary:

Broad-complex tachycardia	
Regular • **Assume ventricular tachycardia (unless previously confirmed SVT with bundle branch block)** • **Loading dose of amiodarone followed by 24 hour infusion**	**Irregular** • **AF with bundle branch block - treat as for narrow complex tachycardia** • **Polymorphic VT (e.g. torsade de pointes) - IV magnesium**
Narrow-complex tachycardia	
Regular • **Vagal manoeuvres followed by IV adenosine** • **If above unsuccessful consider diagnosis of atrial flutter and control rate (e.g. β-blockers)**	**Irregular** • **Probable atrial fibrillation** • **If onset < 48 hr: consider electrical or chemical cardioversion** • **>48 HR: Rate control (e.g. β-blocker or digoxin) and anticoagulation**

Bradycardia and Peri-Arrest: The joint European Resuscitation Council and Resuscitation Council (UK) 2005 guidelines emphasise that the management of bradycardia depends on:

- Identifying the presence of signs indicating hemodynamic compromise - 'adverse signs'
- Identifying the potential risk of asystole

Adverse signs

The following factors indicate hemodynamic compromise and hence the need for treatment:

- Heart rate < 40 bpm
- Systolic blood pressure < 100 mmHg
- Heart failure
- Ventricular arrhythmias requiring suppression

Atropine is the first line treatment in this situation. If this fails to work, or there is the potential risk of asystole then transvenous pacing is indicated

Complete heart block with a narrow complex QRS complex carries the least risk of asystole as the atrioventricular junctional pacemaker may provide a hemodynamically acceptable and stable heart rate

Potential risk of asystole

The following indicate a potential risk of asystole and hence the need for treatment with transvenous pacing:

- Complete ♥ block
- Recent asystole
- Mobitz type II ♥ block
- Symptomatic 2nd degree
- Ventricular pause > 3 seconds

If there is a delay in the provision of transvenous pacing the following interventions may be used:

- Atropine, up to maximum of 3mg
- Transcutaneous pacing
- Adrenaline infusion titrated to response

Complete heart block

Features

- Syncope
- Heart failure
- Regular bradycardia (30-50 bpm)
- Wide pulse pressure
- JVP: cannon waves in neck
- Variable intensity of S1.

Trifasicular Block: The PR interval is grossly prolonged (1st degree block) and there is an RSR complex in V1 (RBBB) and a left anterior hemi-block (LAHB is diagnosed when QRS in lead II is negative). The combination of RBBB, LAHB and long PR interval has been called trifasicular block. Bifascicular and trifascicular block refer to conduction disturbances below the atrioventricular (AV) node in which two or more of the fascicles of the left bundle branch and the right bundle branch are involved. It has been suggested that unexplained syncope in the presence of bifascicular or trifascicular block is an indication for a permanent pacemaker.

Indications for a Temporary Pacemaker

- Symptomatic/hemodynamically unstable bradycardia, not responding to atropine
- Post-**ANTERIOR MI**: type 2 or complete heart block*
- Trifascicular block prior to surgery

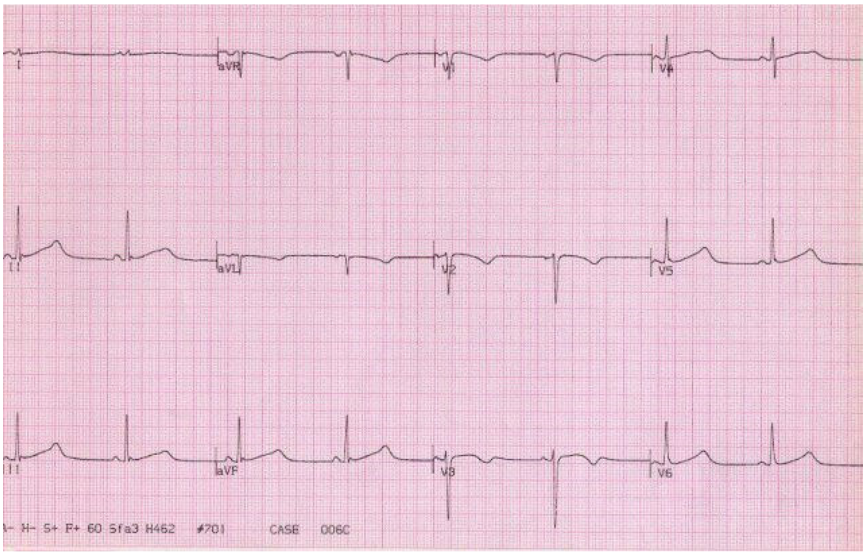
*post-Inferior MI complete heart block is common and can be managed conservatively if asymptomatic and hemodynamically stable

Indications of Implantable Cardiac Defibrillators (IDC):

- Long QT syndrome
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Previous cardiac arrest due to VT/VF
- Previous myocardial infarction with non-sustained VT on 24 hr monitoring, inducible VT on electrophysiology testing and ejection fraction < 35%
- Brugada syndrome

Long QT Syndrome (LQTS) is an inherited condition associated with delayed repolarization of the ventricles. It is important to recognise as it may lead to ventricular tachycardia and can therefore cause collapse/sudden death. The most common variants of LQTS (LQT1 & LQT2) are caused by defects in **α subunit** of the slow delayed rectifier **potassium channel**. A normal corrected QT is less than 440 ms in ♂s and 450 ms in ♀s.

Blockage of K^+ channels causes prolongation of QT



Causes:

Drugs	Congenital	Other causes

• Amiodarone
• Sotalol*
• Class I-a antiarrhythmic
• Tricyclic antidepressants
• Chloroquine
• Terfenadine
• Macrolide (erythromycin)
• Quinolones
	• Jervell-Lange-Nielsen syndrome (includes deafness and is due to an abnormal potassium channel)
	• Romano-Ward syndrome (no deafness)
		• Electrolyte:
		  ○ **Hypocalcemia**
		  ○ **Hypokalemia**
		  ○ **Hypomagnesemia**
		• Acute MI
		• Myocarditis
		• **Hypothermia**
		• Subarachnoid hemorrhage

Features

- May be picked up on routine ECG or following family screening
- Long QT1 - usually associated with exertional syncope, often swimming
- Long QT2 - often associated with syncope occuring following emotional stress, exercise or auditory stimuli
- Long QT3 - events often occur at night or at rest (associated with brady, so pacemaker may be beneficial)
- Long QT4 – associated with Parox. AF
- Sudden cardiac death

Management

- Avoid drugs which prolong QT and other precipitants if appropriate (e.g. Strenuous exercise)
- 1st line pharmacological therapy is Mg^+ IV (bolus then infusion)
- β-blockers**
- Implantable cardioverter defibrillators in high risk cases (if β-blockers fail)
- Left stellate sympathectomy (if β-blockers fail or when there is multiple ICD shocks)

*a non-sedating antihistamine and classic cause of prolonged QT in a patient, especially if also taking P450 enzyme inhibitor, e.g. Patient with a cold takes terfenadine and erythromycin at the same time

**note sotalol may exacerbate long QT syndrome

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a form of inherited cardiovascular disease which may present with syncope or sudden cardiac death. It is generally regarded as the second most common cause of sudden cardiac death in the young after hypertrophic cardiomyopathy.

Pathophysiology

- Inherited in an **autosomal dominant** pattern with variable expression
- The right ventricular myocardium is replaced by fibrofatty tissue

Presentation

- Palpitations
- Syncope
- Sudden cardiac death

Investigation

- ECG abnormalities in **V1-3, typically T wave inversion. An epsilon wave** is found in about 50% of those with ARV - this is best described as a terminal notch in the QRS complex
- Echo changes are often subtle in the early stages but may show an enlarged, hypokinetic right ventricle with a thin free wall
- Magnetic resonance imaging is useful to show fibrofatty tissue

Management

- Drugs: sotalol is the most widely used antiarrhythmic
- Catheter ablation to prevent ventricular tachycardia
- Implantable cardioverter-defibrillator

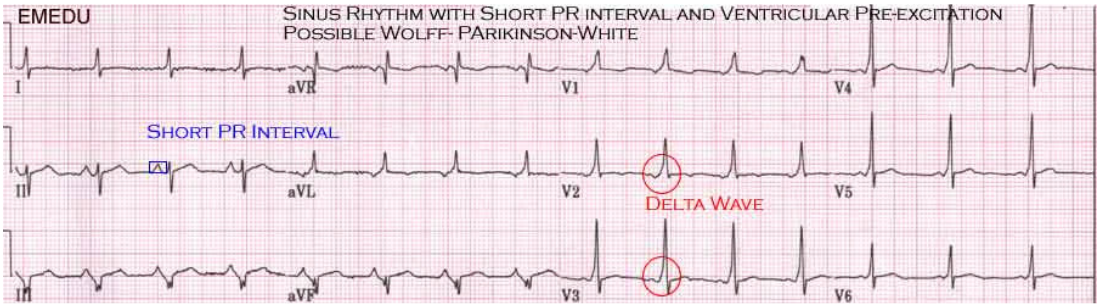
Naxos disease

- An autosomal recessive variant of ARVC
- A triad of ARVC, palmoplantar keratosis, and woolly hair

Wolff-Parkinson White (WPW) syndrome is caused by a congenital accessory conducting pathway between the atria and ventricles leading to atrioventricular re-entry tachycardia (AVRT). As the accessory pathway does not slow conduction AF can degenerate rapidly to VF

Possible ECG features include:

- Short PR interval
- Wide QRS complexes with a slurred upstroke - 'delta wave'
- Left axis deviation if right-sided accessory pathway*
- Right axis deviation if left-sided accessory pathway*



Differentiating between type A and type B

- Type A (left-sided pathway): dominant R wave in V1, seen in the above ECG.
- Type B (right-sided pathway): no dominant R wave in V1

Associations of WPW

- HOCM
- Mitral valve prolapse
- Ebstein's anomaly
- Thyrotoxicosis
- Secundum ASD

Management

- Definitive treatment: radiofrequency ablation of the accessory pathway
- Medical therapy: sotalol**, amiodarone, flecainide
- For cardioversion: Flecainide is superior to Amiodarone

*in the majority of cases, or in a question without Specification, Wolff-Parkinson-White syndrome is associated with left axis deviation

****sotalol should be avoided** if there is coexistent atrial fibrillation as prolonging the refractory period at the AV node may ↑ the rate of transmission through the accessory pathway, increasing the ventricular rate and potentially deteriorating into ventricular fibrillation. **Adenosine should be avoided** as blocking the AV node can paradoxically ↑ ventricular rate resulting in fall in cardiac output. **Verapamil and digoxin should also be avoided** in patients with Wolff-Parkinson White as they may precipitate VT or VF.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a form of inherited cardiac disease associated with sudden cardiac death. It is inherited in an autosomal dominant fashion and has a prevalence of around 1:10,000.

Pathophysiology

- The most common cause is a defect in the ryanodine receptor (RYR2) which is found in the myocardial sarcoplasmic reticulum

Features

- Exercise or emotion induced polymorphic ventricular tachycardia resulting in syncope
- Sudden cardiac death
- Symptoms generally develop before the age of 20 years

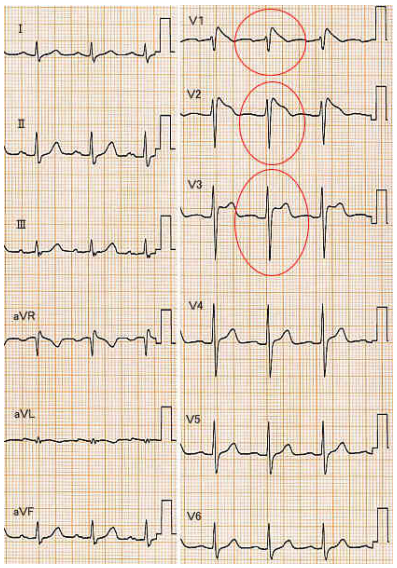
Management

- β-blockers
- Implantable cardioverter-defibrillator

Brugada syndrome is a form of inherited cardiovascular disease with may present with sudden cardiac death. It is inherited in an autosomal dominant fashion and has an estimated prevalence of 1:5,000-10,000. Brugada syndrome is more common in Asians.

Pathophysiology

- A large number of variants exist
- Around 20-40% of cases are caused by a mutation in the SCN5a gene which encodes the **myocardial sodium ion channel protein**



ECG changes

- Convex ST elevation V1-V3
- Partial right bundle branch block
- Changes may be more apparent following flecainide

Ajmaline (class Ia antiarrhythmic) is used to unmaks hidden Brugada

Management

- Implantable cardioverter-defibrillator
- Quinidine is useful in VF storm (indicated by fast repeated ICD shocks)

CARDIOMYOPATHIES

Hypertrophic Obstructive Cardiomyopathy (HOCM) is an autosomal dominant disorder of muscle tissue caused by defects in the genes encoding contractile proteins. The estimated prevalence is 1 in 500. Mutations to various proteins including β-myosin, α-tropomyosin and troponin T have been identified. Septal hypertrophy causes left ventricular outflow obstruction. It is an important cause of sudden death in apparently healthy individuals.

Hypertrophic obstructive cardiomyopathy (HOCM) is a more common cause of sudden cardiac death than arrhythmogenic right ventricular dysplasia (ARVD) ← 2nd most common

Features

- Often asymptomatic
- Dyspnea, angina, syncope
- Sudden death (most commonly due to ventricular arrhythmias), arrhythmias, heart failure
- Jerky pulse, large 'a' waves, double apex beat
- Ejection systolic murmur: ↑ with valsalva manoeuvre and ↓ on squatting

Associations

- Friedreich's ataxia
- Wolff-Parkinson White

ECG

- Left ventricular hypertrophy (LVH)
- Atrial enlargement (abnormal P morphology)
- Progressive T wave inversion
- ST-T abnormalities
- Deep Q waves
- Axis deviation
- Prolonged PR or sinus bradycardia
- BBB (bundle brach block)
- Ectopic atrial rhythm
- Atrial fibrillation may occasionally be seen

Echo (Mr. Sam Ash):

- Mitral regurgitation **(MR)**
- Systolic anterior motion **(SAM)** of the anterior mitral valve leaflet
- Asymmetric hypertrophy **(ASH)**

Part II Tip If LVOT gradient < 35 with signs of heart failure → responds well to β blockers

LVOT: Left Ventriculat Outflow Tract – (the gradient is caused by SAM as the leaflet blocks the outflow)
Even with good response on β blockers patients would still need ICD

Poor prognostic factors

- Syncope
- Family history of sudden death
- Young age at presentation
- Non-sustained ventricular tachycardia on 24 or 48-hour holter monitoring

- Abnormal blood pressure changes on exercise
- ↑ Septal wall thickness, > 3cm

Management

- **A**miodarone
- **β**-blockers or verapamil for symptoms
- **C**ardioverter defibrillator
- **D**ual chamber pacemaker
- **E**ndocarditis prophylaxis

Drugs to avoid

- Nitrates
- ACE-inhibitors
- Inotropes
- Digoxin is contraindicated if there is significant LVOT gradient

Dilated Cardiomyopathy (DCM)

Basics:

- Prevelance is 1% in adult – it ↑ to 10% at age of 80 yrs
- Annual mortality of cardiomyopathies and HF is 20%
- Dilated heart leading to systolic (+/- diastolic) dysfunction
- All 4 chambers affected but LV more than RV
- Features include arrhythmias, emboli, mitral regurgitation
- Absence of congenital, valvular or ischemic heart disease

Causes often considered separate entities

- Alcohol: may improve with thiamine (best prognosis after removing the cause)
- Peripartum
- Hypertension

Other causes

- Inherited (see below)
- Infections e.g. Coxsackie A and B, HIV, diphtheria, parasitic
- Endocrine e.g. Hyperthyroidism
- Infiltrative* e.g. Hemochromatosis, sarcoidosis
- Neuromuscular e.g. Duchenne muscular dystrophy
- Nutritional e.g. Kwashiorkor, pellagra, thiamine/selenium deficiency
- Drugs e.g. Doxorubicin

Inherited dilated cardiomyopathy

- Around a third of patients with DCM are thought to have a genetic predisposition
- A large number of heterogeneous defects have been identified
- The majority of defects are inherited in an autosomal dominant fashion although other patterns of inheritance are seen

*these causes may also lead to restrictive cardiomyopathy

Restrictive Cardiomyopathy

Features

- Similar to constrictive pericarditis

Restrictive cardiomyopathy vs Constrictive pericarditis, in restrictive:

- Prominent apical pulse
- Absence of pericardial calcification on CXR
- Heart may be enlarged
- ECG abnormalities e.g. Bundle branch block, Q waves

Causes

- **Amyloidosis (e.g. Secondary to myeloma) - most common cause in UK**
- Hemochromatosis
- Loffler's syndrome
- Sarcoidosis
- Scleroderma

Atrial Myxoma:

Overview

- 75% occur in left atrium
- More common in ♀s

Features

- Systemic: weight loss, fever, clubbing
- Emboli
- Atrial fibrillation
- Mid-diastolic murmur, 'tumour plop'

Valvular Abnormalities

Aortic Stenosis (AS):

Features of severe AS:

- Narrow pulse pressure
- Slow rising pulse
- Delayed ESM
- Soft/absent S2
- S4
- Thrill
- Duration of murmur
- Left ventricular hypertrophy or failure

Left ventricular systolic dysfunction will result in a ↓ flow-rate across the aortic valve and hence a quieter murmur and low gradient on Echo

Causes of AS

- **Degenerative calcification (most common cause in elderly patients)**
- **Bicuspid aortic valve (most common cause in younger patients)**
- William's syndrome (supravalvular aortic stenosis)
- Post-rheumatic disease
- Subvalvular: HOCM

Aortic stenosis management: AVR if symptomatic, otherwise cut-off is gradient of 50 mmHg

Part II Tip

- Dobutamine echo is used to assess the severity of AS in severe LVSF impairment
- Patients with >20% increase in stroke volume after dobutamine means better prognosis post surgery compared to those with no LV contractile reserve.

Management

- If asymptomatic then observe the patient is general rule
- If symptomatic then valve replacement
- If asymptomatic but valvular gradient > 50 mmHg and with features such as left ventricular systolic dysfunction then consider surgery
- Balloon valvuloplasty is limited to patients with critical aortic stenosis who are not fit for valve replacement

Part II Tip

Heyde's syndrome: a well-known association between microcytic anemia and calcific AS. The treatment is to replace the valve, as the mechanism is thought to be due to destruction of von Willebrand's factor as the platelets traverse the stenosed valve resulting in bleeding per rectum. The investigation of choice after valve replacement is mesenteric angiography as the bleeding vessels are poorly visualised on colonoscopy. This would look for the presence of angiodysplasia, which may be associated with aortic stenosis. Resection of the diseased bowel has also been described as a treatment. There is an association with AS; this is thought to be due to microangiopathic hemolysis. Hemodynamic optimisation prior to surgery with blood transfusion is preferred but this would depend on the surgeon.

Aortic Regurgitation (AR):

Features

- Early diastolic murmur
- Collapsing pulse
- Wide pulse pressure
- Mid-diastolic Austin-Flint murmur in severe AR - due to partial closure of the anterior mitral valve cusps caused by the regurgitation streams

Causes (due to valve disease)

- Rheumatic fever
- Infective endocarditis
- Connective tissue diseases e.g. RA/SLE
- Bicuspid aortic valve

Causes (due to aortic root disease)

- Aortic dissection
- Spondylarthropathies (e.g. Ankylosing spondylitis)
- Hypertension
- Syphilis
- Marfan's, Ehler-Danlos syndrome

Part II Tip

Management:

Asymptomatic with LVSF <50% + dilated LV (EDD > 75mm – ESD>55mm)

↓

Consider AVR (Aortiv Valve Replacement)

Mitral Valve Prolapse

Mitral Valve Prolapse is common, occurring in around 5-10 % of the population. It is usually idiopathic but may be associated with a wide variety of cardiovascular disease and other conditions

Associations

- Congenital heart disease: PDA, ASD
- Cardiomyopathy
- Turner's syndrome
- Marfan's syndrome, Fragile X
- Osteogenesis imperfecta
- Pseudoxanthoma elasticum
- Wolff-Parkinson White syndrome
- Long-QT syndrome

Features

- Patients may complain of atypical chest pain or palpitations
- Mid-systolic click (occurs later if patient squatting)
- Late systolic murmur (longer if patient standing)
- Complications: mitral regurgitation, arrhythmias (including long QT), emboli, sudden death

Management:

- Patients > 75 years who are in AF or with LVSF impairment, should be referred to surgical assessment as early as possible
- TOE (transesophageal echo)can tell if the valve is for repair or replacement, can be done intra-operatily
- Follow up is crucial as 15% of MVP patients develop the most serious complication after 15 years period of being prolapsed (TIA, Ischemic Stokes)
- Mild to moderate MVP with normal LVSF → β blockers + echo follow up every 2-3 years

Mitral Stenosis:

it is said that the **causes of mitral stenosis are rheumatic fever, rheumatic fever and rheumatic fever**. Rarer causes that may be seen in the MRCP include mucopolysaccharidoses, carcinoid and endocardial fibroelastosis

Features

- Mid-diastolic murmur (best heard in expiration)
- Loud S1, opening snap
- Low volume pulse
- Malar flush
- Atrial fibrillation

Features of severe MS

- Length of murmur ↑
- Opening snap becomes closer to S2

Echocardiography

- The normal cross sectional area of the mitral valve is 4-6 cm^2. A 'tight' mitral stenosis implies a cross sectional area of < 1 cm^2.

Percutaneous Balloon Valvotomy: used to treat sever M.S. it is contraindicatin:

- Moderate to severe mitral regurgitation
- Left atrial thrombus
- Heavily calcified mitral valve
- Concomitant coronary artery or other valve disease requiring surgery.

Part II Tip

Lutembacher's syndrome: is a syndrome characterized by both MS & ASD. Both conditions may be congenital and occur concurrently, or the MS may occur as a result of rheumatic fever or other cause. Incidence of Lutembacher's syndrome is higher in women due to the higher incidence of congenital ASD. Cardiac signs are mixed due to the two concurrent lesions. Presentation is typically in later life, with fatigue or atrial fibrillation. Ideally, surgery should be performed as early as possible due to the risks of Eisenmenger's syndrome if untreated.

Tricuspid Regurgitation:

Signs

- Pan-systolic murmur
- Giant v waves in JVP
- Pulsatile hepatomegaly
- Left parasternal heave

Causes

- Right ventricular dilation
- Pulmonary hypertension e.g. COPD
- Rheumatic heart disease
- Infective endocarditis (especially intravenous drug users)
- Ebstein's anomaly
- Carcinoid syndrome

Prosthetic Valves: the most common valves which need replacing are the aortic and mitral valve. There are two main options for replacement: biological (bioprosthetic) or mechanical.

Biological (bioprosthetic) valves	Mechanical valves
Usually bovine or porcine in origin Major disadvantage is structural deterioration and calcification over time. Most older patients (> 65 years for aortic valves and > 70 years for mitral valves) receive a bioprosthetic valve Long-term anticoagulation not usually needed. Warfarin may be given for the first 3 months depending on patient factors. Low-dose aspirin is given long-term.	The most common type now implanted is the bileaflet valve. Ball-and-cage valves are rarely used nowadays Mechanical valves have a low failure rate Major disadvantage is the increased risk of thrombosis meaning long-term anticoagulation is needed. Aspirin is normally given in addition unless there is a contraindication. Target INR • Aortic: 2.0-3.0 • Mitral: 2.5-3.5

Following the 2008 NICE guidelines for prophylaxis of endocarditis antibiotics are no longer recommended for common procedures such as dental work

Prosthetic Valve Thrombosis (PVT): This complication occurs in 0.03 to 5.5% annually with equal frequency in bioprosthesis and mechanical valves. It is more common in mitral prosthesis and with subtherapeutic anticoagulation, this resulting in shock.

Diagnosis:

- The best diagnostic modality is transoesophageal echocardiography
- Transthoracic echocardiography is the initial choice in sick patients, and if adequate visualisation is not obtained TEE can be done.

Mangement:

- Thrombolytic therapy should be given for patients in pulmonary edema or hypotension.
- In stable patients, surgery is a better option for left-sided PVT, while right-sided PVT should be treated with thrombolytic agents.
- Serial echocardiography should be performed, and if the response is inadequate repeat thrombolytic therapy can be given.

Major Vessels Abnormalities

Aortic Disection:

Aortic dissection
- Type A - ascending aorta - control BP(IV labetalol) + surgery
- Type B - descending aorta - control BP(IV labetalol)

Type A	Type B
Ascending aorta (2/3 of cases)	Descending aorta, distal to left subclavian origin
Management	
• Surgical management, but blood pressure should be controlled to a target systolic of 100-120 mmHg whilst awaiting intervention, by **IV Labetalol**	• Conservative management • Bed rest • ↓ blood pressure **IV labetalol** to prevent progression

*endovascular repair of type B aortic dissection may have a role in the future

Associations
- Hypertension
- Trauma
- Bicuspid aortic valve
- Collagens: marfan's syndrome, ehlers-danlos syndrome
- Turner's and noonan's syndrome
- Pregnancy
- Syphilis

Complications of backward tear
- Aortic incompetence/regurgitation
- MI: inferior pattern often seen due to right coronary involvement

Complications of forward tear
- Unequal arm pulses and BP
- Stroke
- Renal failure

Primary Pulmonary Hypertension:

the classification of pulmonary hypertension is currently changing with the term idiopathic pulmonary arterial hypertension (IPAH) becoming more widely used

Secondary causes of pulmonary hypertension include COPD, congenital heart disease (Eisenmenger's syndrome), recurrent pulmonary embolism, HIV and sarcoidosis.

Primary pulmonary hypertension (PPH, now IPAH)
- Pulmonary arterial pressure > 25 mmHg at rest, > 30mmHg with exercise
- PPH is diagnosed when no underlying cause can be found
- Around 10% of cases are familial: autosomal dominant
- Endothelin thought to play a key role in pathogenesis
- Associated with HIV, cocaine and anorexigens (e.g. Fenfluramine)

Features

- More common in ♀s, typically presents at 20-40 years old
- Progressive SOB
- Cyanosis
- Right ventricular heave, loud P2, raised JVP with prominent 'a' waves, tricuspid regurgitation

Management

- Diuretics if right heart failure
- Anticoagulation
- Vasodilator therapy: calcium channel blocker, IV prostaglandins, bosentan: endothelin-1 receptor antagonist
- Heart-lung transplant

Pulmonary Arterial Hypertension (PAH) may be defined as a sustained elevation in mean pulmonary arterial pressure of greater than 25 mmHg at rest or 30 mmHg after exercise.

Features

- Exertional dyspnea is the most frequent symptom
- Chest pain and syncope may also occur
- Loud P2
- Left parasternal heave (due to right ventricular hypertrophy)

PAH has recently been reclassified by the WHO:

Group 1: Pulmonary arterial hypertension (PAH)
• Idiopathic* • Familial • Associated conditions: collagen vascular disease, congenital heart disease with systemic to pulmonary shunts, HIV**, drugs and toxins, sickle cell disease • Persistent pulmonary hypertension of the newborn
Group 2: Pulmonary hypertension with left heart disease
left-sided atrial, ventricular or valvular disease such as left ventricular systolic and diastolic dysfunction, mitral stenosis and mitral regurgitation
Group 3: Pulmonary hypertension secondary to lung disease/hypoxia
• COPD • Interstitial lung disease • Sleep apnoea • High altitude
Group 4: Pulmonary hypertension due to thromboembolic disease
Sickle cell, Polycythemia ..etc
Group 5: Miscellaneous conditions
Lymphangiomatosis e.g. secondary to carcinomatosis or sarcoidosis

*previously termed primary pulmonary hypertension
**the mechanism by which HIV infection produces pulmonary hypertension remains unknown

Whilst echocardiography may strongly point towards a diagnosis of pulmonary hypertension all patients need to have right heart pressures measured. **Cardiac catheterisation is therefore the single most important investigation**.

Management should first involve treating any underlying conditions, for example with anticoagulants or oxygen. Following this, it has now been shown that **acute vasodilator testing** is central to deciding on the appropriate management strategy. Acute vasodilator testing aims to decide which patients show a significant fall in pulmonary arterial pressure following the administration of vasodilators such as intravenous epoprostenol or inhaled nitric oxide

If there is a positive response to acute vasodilator testing

- Oral calcium channel blockers

If there is a negative response to acute vasodilator testing

- Prostacyclin analogues: treprostinil, ilioprost
- Endothelin receptor antagonists: bosentan
- Phosphodiesterase inhibitors: sildenafil

Congenital Heart Diseases

Congenital heart disease
- Cyanotic: TGA most common at birth, Fallot's most common overall
- Acyanotic: VSD most common cause

Tetralogy of Fallot is more common than transposition of the great arteries (TGA), Fallot's doesn't usually present until 1-2 months following the identification of a murmur or cyanosis. **In newborn, TGA is the most common presenting cause of cyanotic congenital heart disease**.

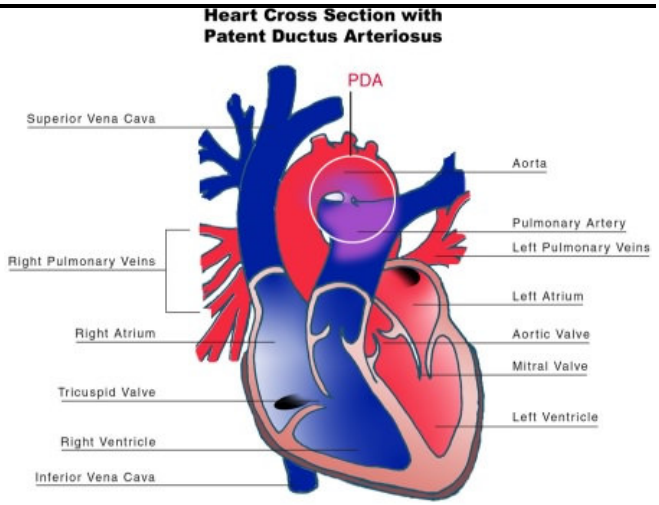
Acyanotic - most common causes
- Ventricular septal defects (VSD) - most common, accounts for 30%
- Atrial septal defect (ASD)
- Patent ductus arteriosus (PDA)
- Coarctation of the aorta
- Aortic valve stenosis

VSDs are more common than ASDs. However, in adult patients ASDs are the more common new diagnosis as they generally presents later

Cyanotic - most common causes
- Tetralogy of Fallot
- Transposition of the great arteries (TGA)
- Tricuspid atresia
- Pulmonary valve stenosis

Patent Ductus Arteriosus (PDA)

Overview
- acyanotic congenital heart defect
- connection between the pulmonary trunk and descending aorta
- more common in premature babies, born at high altitude or maternal rubella infection in the first trimester



Features
- Left subclavicular thrill
- Continuous 'machinery' murmur

- Large volume, collapsing pulse
- Wide pulse pressure
- Heaving apex beat

Management
- Indomethacin closes the connection in the majority of cases
- If associated with another congenital heart defect amenable to surgery then prostaglandin E1 is useful to keep the duct open until after surgical repair

Ventricular Septal Defects (VSD) are the most common cause of congenital heart disease. They close spontaneously in around 50% of cases. Non-congenital causes include post myocardial infarction

Features

- Classically a pan-systolic murmur which is louder in smaller defects

Complications

- Aortic regurgitation*
- Infective endocarditis
- Eisenmenger's complex
- Right heart failure

Part II Tip

Fick equation

In VSD with left to right shunt, the shunt ratio can be calculated using the Fick equation:

$$\frac{Qp}{Qs} = \frac{Ao - MV}{PV - PA}$$

Where Qp = pulmonary flow, Qs = systemic flow, Ao = aortic saturation, MV = mixed venous saturation, PV = pulmonary vein saturation (assumed to be 97%) and PA = pulmonary artery saturation.

When

- Qp/Qs > 2.0 → Surgery for children
- Qp/Qs > 1.5 → Surgery for Adult

*aortic regurgitation is due to a poorly supported right coronary cusp resulting in cusp prolapsed. AF is associated with ASD.

Atrial Septal Defects (ASDs) are the most likely congenital heart defect to be found in adulthood. They carry a significant mortality, with 50% of patients being dead at 50 years. Two types of ASDs are recognised, ostium secundum and ostium primum. **Ostium secundum are the most common**

Features

- Ejection systolic murmur, fixed splitting of S2
- Embolism may pass from venous system to left side of heart causing a stroke

Ostium secundum (70% of ASDs)

- Associated with Holt-Oram syndrome (tri-phalangeal thumbs)
- ECG: **RBBB with RAD** (secondum).

Ostium primum

- Present earlier than ostium secundum defects
- Associated with abnormal AV valves
- ECG: **RBBB with LAD**, prolonged PR interval

Patent foramen ovale (PFO) is present in around 20% of the population. It may allow embolus (e.g. from DVT) to pass from right side of the heart to the left side leading to a stroke - 'a paradoxical embolus'. **It's the most common cause of stroke following DVT**.

DO TOE (Transesophageal echocardiography)

There also appears to be an association between migraine and PFO. Some studies have reported improvement in migraine symptoms following closure of the PFO

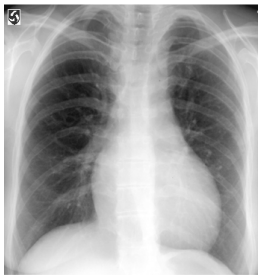
Coarctation of the Aorta describes a congenital narrowing of the descending aorta, it is more common in ♂s (despite association with Turner's syndrome). Surgical repair is the treatment, but even with repair sometimes recurrence happen.

Features

- Infancy: heart failure
- Adult: hypertension
- Radio-femoral delay
- Mid or late systolic murmur, maximal over back
- Apical click from the aortic valve
- Notching of the inferior border of the ribs (due to collateral vessels) is not seen in young children

Associations

- Turner's syndrome
- Bicuspid aortic valve
- Berry aneurysms
- Neurofibromatosis
- Accelerated Coronary Artesry Disease (CAD)



Eisenmenger's Syndrome is characterized by the reversal of the left-right shunt due to pulmonary hypertension. The original murmur may disappear once Eisenmenger's syndrome develops.

Associated with

- VSD
- ASD
- PDA

Features

- Original murmur may disappear
- Cyanosis
- Clubbing
- Right ventricular failure
- Hemoptysis, embolism

Management

- Heart-lung transplantation is required

Bicuspid Aortic Valve:

Overview

- Occurs in 1-2% of the population
- Usually asymptomatic in childhood
- The majority eventually develop aortic stenosis or regurgitation
- Associated with a **left dominant coronary circulation** (the posterior descending artery arises from the circumflex instead of the right coronary artery) and **turner's syndrome**
- Around 5% of patients also have coarctation of the aorta

Complications

- Aortic stenosis/regurgitation.
- Higher risk for aortic dissection and aneurysm formation of the ascending aorta

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Tetralogy of Fallot (TOF) is the most common cause of cyanotic congenital heart disease*. It typically presents at around 1-2 months, although may not be picked up until the baby is 6 months old

The four characteristic features are:

- Ventricular septal defect (VSD)
- Right ventricular hypertrophy
- Right ventricular outflow tract (RVOT) obstruction, pulmonary stenosis
- Overriding aorta

The severity of RVOT obstruction determines the degree of cyanosis and severity

Other features

- Cyanosis
- Causes a right-to-left shunt
- Ejection systolic murmur due to pulmonary stenosis (the VSD doesn't usually cause a murmur)
- A right-sided aortic arch is seen in 25% of patients
- Chest x-ray shows a 'boot-shaped' heart, ECG shows right ventricular hypertrophy

Management

- Surgical repair is often undertaken in two parts
- Cyanotic episodes may be helped by β-blockers to ↓ infundibular spasm

*however, at birth transposition of the great arteries is the more common lesion as patients with TOF generally present at around 1-2 months

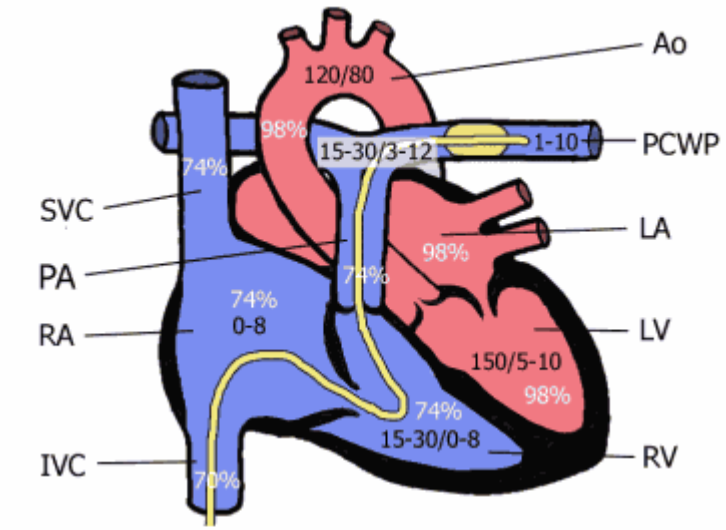
---

Dextrocardia: is a rare condition and occurs with in frequency in ♂:♀.

Classical ECG features:

- Inverted P in lead I
- Shift of the P axis (usually about +120 degrees) and reversed R wave progression.
- Reverse placement of the praecordial leads on the right chest at sites corresponding to the left chest positions corrects this trend.

Typically patients have a normal life expectancy if no cardiac anomalies are present.



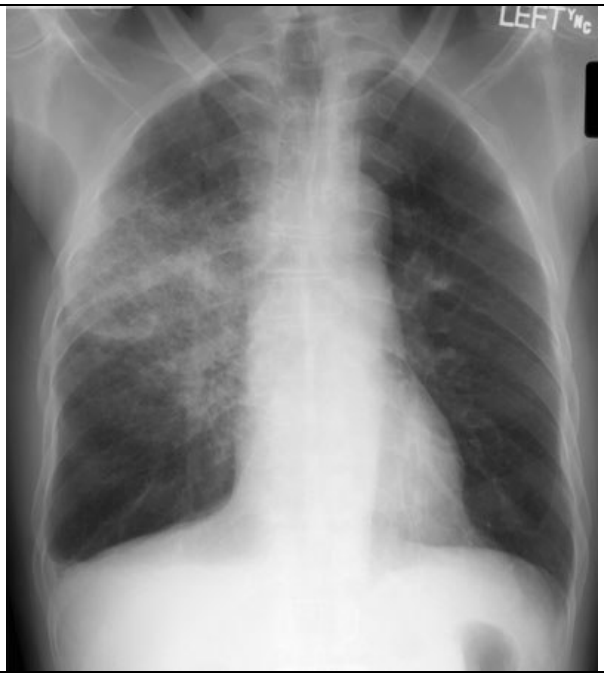
Cardiac catheter data
Normal cardiac pressures & oxygen saturation

	End systolic (mmHg)	End diastolic (mmHg)	Mean	O_2 saturation
Left heart				
Aorta	120	80	95	98%
LV	150	5-10		98%
LA				98%
Right heart				
RA			0-8	74%
RV	15-30	0-8		74%
PA	15-30	3-12	9-16	74%
SVC				74%
IVC				70%
PCWP			1-10	

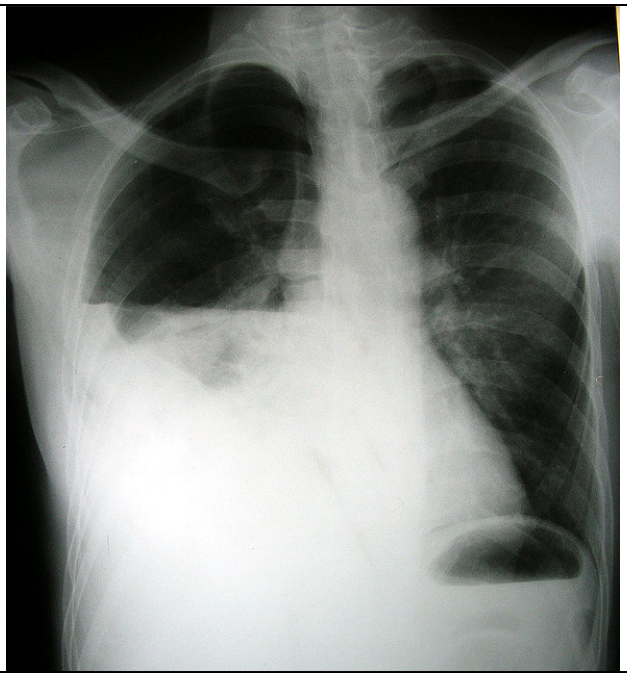
- **Patent Ductus Arteriosus:** an unexpected ↑ in O_2 saturation between the RV and PA; this is associated with high pulmonary artery pressures and a high wedge pressure
- **VSD:** ↑ in O_2 saturation between LA and LV, indicating right to left shunt at the level of the ventricles.
- **Pulmonary stenosis:** RV systolic >> PA systolic (Gradient is RV Systolic – PA Systolic)

  Pulmonary stenosis is:
  - **Mild**: valve area > 1 cm/m^2. gradient is 50-80 mmHg, or RV systolic < 75 mmHg
  - **Moderate:** valve area 0.5-1 & gradient is 50-80, or RV systolic: 75-100
  - **Severe:** valve area < 0.5, and gradient > 80 mmHg
- **RVH:** RV pressures ↑ (>30).
- **Right to left ventricular shunt:** indicated by the oxygen saturations in LV & RV
- **Over-Riding Aorta:** there is ↓ in oxygen saturation between the LV and aorta. This could occur in either Fallot's or with a PDA with right to left shunting.

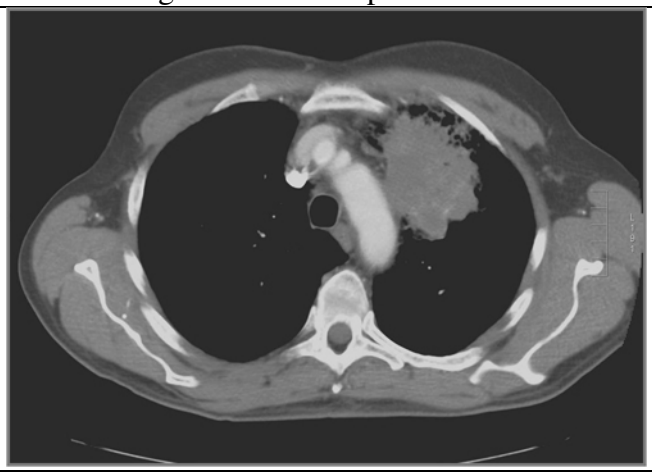
PULMONOLOGY



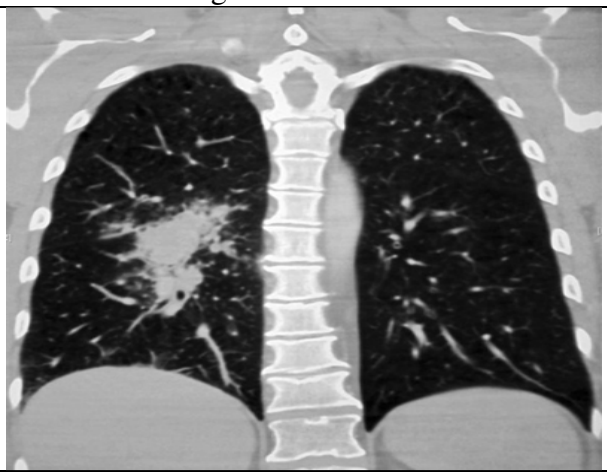
right middle lobe pneumonia



right hemothorax



CT Chest showing tumor



CT Chest showing tumor

Respiratory Physiology:

Control of respiration

- Central regulatory centres
- Central and peripheral chemoreceptors
- Pulmonary receptors

Central regulatory centres

- Medullary respiratory centre
- Apneustic centre (lower pons)
- Pneumotaxic centre (upper pons)

Central and peripheral chemoreceptors

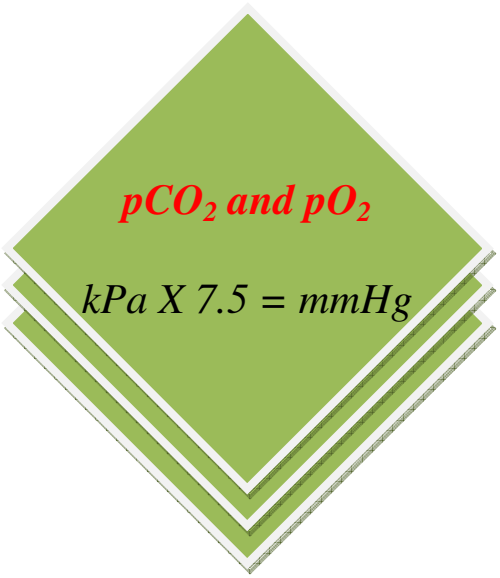
- Central: raised [H+] in ECF stimulates respiration
- Peripheral: carotid + aortic bodies, respond to raised pCO_2 & $[H^+]$, lesser extent low pO_2

Pulmonary receptors

- Stretch receptors, lung distension causes slowing of respiratory rate (Hering-Bruer reflex)
- Irritant receptor, leading to bronchoconstriction
- Juxtacapillary receptors, stimulated by stretching of the microvasculature

Chloride shift

- CO_2 diffuses into RBCs
- $CO_2 + H_2O$ ---- carbonic anhydrase $\rightarrow HCO_3^- + H^+$
- H^+ combines with Hb
- HCO_3^- diffuses out of cell,- Cl^- replaces it



Bohr Effect

- Increasing acidity (or pCO_2) means O_2 binds less well to Hb

Haldane effect

- ↑ pO_2 means CO_2 binds less well to Hb

Tidal Volume (TV)

- Volume inspired or expired with each breath at rest
- 500ml in ♂s, 350ml in ♀s

Inspiratory Reserve Volume (IRV) = 2-3 L

- Maximum volume of air that can be inspired after normal tidal inspiration
- Inspiratory capacity = TV + IRV

Expiratory Reserve Volume (ERV) = 750ml

- Maximum volume of air that can be expired after normal tidal expiration

Residual volume (RV) = 1.2L

- Volume of air remaining after maximal expiration
- ↑ with age
- RV = FRC – ERV (Functional Residual Capacity - Expiratory Reserve Volume)

Vital Capacity (VC) = 5L

- Maximum volume of air that can be expired after a maximal inspiration
- 4,500ml in ♂s, 3,500 mls in ♀s
- ↓ with age
- VC = IC + ERV

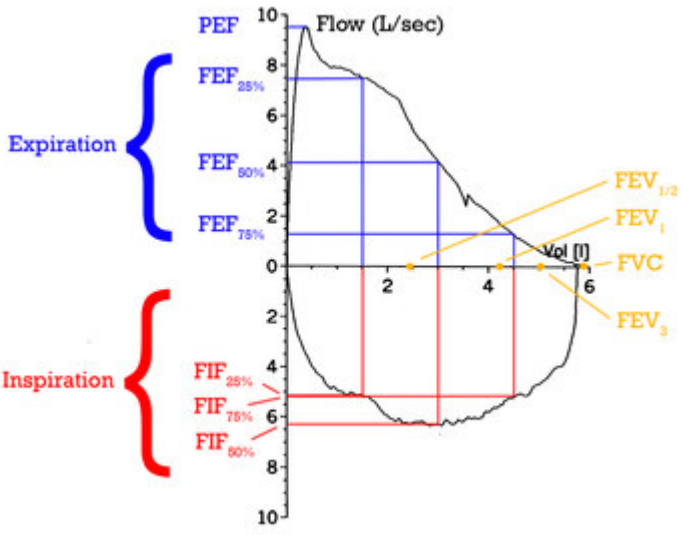
Total lung capacity (TLC) is the sum of the vital capacity + residual volume

Abbreviation	Name	Description
FVC	Forced Vital Capacity	This is the volume of air that can forcibly be blown out after full inspiration, measured in liters.
FEV_1	Forced Expiratory Volume in 1 Second	This is the maximum volume of air that can forcibly blow out in the first second during the FVC manoeuvre, measured in liters. Along with FVC it is considered one of the primary indicators of lung function.
FEV_1/FVC	FEV_1%	This is the ratio of FEV_1 to FVC. In healthy adults this should be approximately 75–80%.
PEF	Peak Expiratory Flow	This is the maximal flow (or speed) achieved during the maximally forced expiration initiated at full inspiration, measured in liters per second.
FEF 25–75% or 25–50%	Forced Expiratory Flow 25–75% or 25–50%	This is the average flow (or speed) of air coming out of the lung during the middle portion of the expiration (also sometimes referred to as the MMEF, for maximal mid-expiratory flow).
FIF 25–75% or 25–50%	Forced Inspiratory Flow 25–75% or 25–50%	This is similar to FEF 25–75% or 25–50% except the measurement is taken during inspiration.
FET	Forced Expiratory Time	This measures the length of the expiration in seconds.
SVC	Slow Vital capacity	Maximum volume of air that can be exhaled slowly after slow maximum inhalation.
Vt	Tidal volume	During the respiratory cycle, a specific volume of air is drawn into and then expired out of the lungs. This volume is tidal volume.
MVV	Maximum Voluntary Ventilation	A measure of the maximum amount of air that can be inhaled and exhaled in one minute, measured in liters/minute.

Note that functional residual capacity (FRC) cannot be measured via spirometry, but it can be measured with a plethysmograph.

Measurement	Value (♂/♀)	Calculation	Description
Total lung capacity (TLC)	= 6.0 / 4.7 L	= IRV + Vt + ERV + RV	The volume of air contained in the lung at the end of maximal inspiration. The total volume of the lung (the volume of air in the lungs after maximum inspiration).
Vital capacity (VC)	= 4.6 / 3.6 L	= IRV + Vt + ERV	The amount of air that can be forced out of the lungs after a maximal inspiration. Emphasis on completeness of expiration. The maximum volume of air that can be voluntarily moved in and out of the respiratory system
Forced vital capacity (FVC)	= 4.8 / 3.7 L	measured	The amount of air that can be maximally forced out of the lungs after a maximal inspiration. Emphasis on speed
Tidal volume (Vt)	= 500 / 390 mL	measured	The amount of air breathed in or out during normal respiration. The volume of air an individual is normally breathing in and out.
Residual volume (RV)	= 1.2 / 0.93 L	measured	The amount of air left in the lungs after a maximal exhalation. The amount of air that is always in the lungs and can never be expired (i.e.: the amount of air that stays in the lungs after maximum expiration).
Expiratory reserve volume (ERV)	= 1.2 / 0.93 L	measured	The amount of additional air that can be pushed out after the end expiratory level of normal breathing. (At the end of a normal breath, the lungs contain the residual volume plus the expiratory reserve volume, or around 2.4 litres. If one then goes on and exhales as much as possible, only the residual volume of 1.2 litres remains).
Inspiratory reserve volume (IRV)	= 3.0 / 2.3 L	measured IRV=VC-(TV+ERV)	The additional air that can be inhaled after a normal tidal breath in. The maximum volume of air that can be inspired in addition to the tidal volume.
Functional residual capacity (FRC)	= 2.4 / 1.9 L	= ERV + RV	The amount of air left in the lungs after a tidal breath out. The amount of air that stays in the lungs during normal breathing.
Inspiratory capacity (IC)	= 3.5 / 2.7 L	= TV + IRV	The maximal volume that can be inspired following a normal expiration.
Anatomical dead space	= 150 / 120 mL	measured	The volume of the conducting airways. Measured with Fowler method.
Physiologic dead volume	= 155 / 120 mL	$V_T \frac{P_{A\,CO_2} - P_{E\,CO_2}}{P_{A\,CO_2}}$	The anatomic dead space plus the alveolar dead space.

Flow-Volume loop showing successful FVC maneuver. Positive values represent expiration, negative values represent inspiration. The trace moves clockwise for expiration followed by inspiration. (Note the FEV_1, $FEV_{1/2}$ and FEV_3 values are arbitrary in this graph and just shown for illustrative purposes, they must be recorded as part of the experiment).



Pulmonary function tests can be used to determine whether a respiratory disease is obstructive or restrictive. The table below summarises the main findings and gives some example conditions:

Obstructive lung disease	Restrictive lung disease
FEV1 - significantly ↓ FVC - ↓ or **normal** (FEV1/FVC) - ↓	FEV1 - ↓ FVC - significantly ↓ (FEV1/FVC) - normal or ↑
Asthma COPD Bronchiectasis Bronchiolitis obliterans	Pulmonary fibrosis Asbestosis Sarcoidosis Acute respiratory distress syndrome Infant respiratory distress syndrome Kyphoscoliosis Neuromuscular disorders

Lung compliance is defined as change in lung volume per unit change in airway pressure

Causes of ↑ compliance	Causes of ↓ compliance
• Age • Emphysema	• Pulmonary edema • Pulmonary fibrosis • Pneumonectomy • Kyphosis

Oxygen dissociation curve

- Shifts **R**ight - **R**aised oxygen delivery - **R**aised acidity, Temp, 2-3 DPG
- Shifts **L**eft - **L**ower oxygen delivery - **L**ower acidity, Temp, 2-3 DPG - also HbF, carboxy/methemoglobin

Oxygen Dissociation Curve describes the relationship between the percentage of saturated hemoglobin and partial pressure of oxygen in the blood. **It is not affected by hemoglobin concentration**, but affected by its quality (HbF, methemoglobin).

Basics

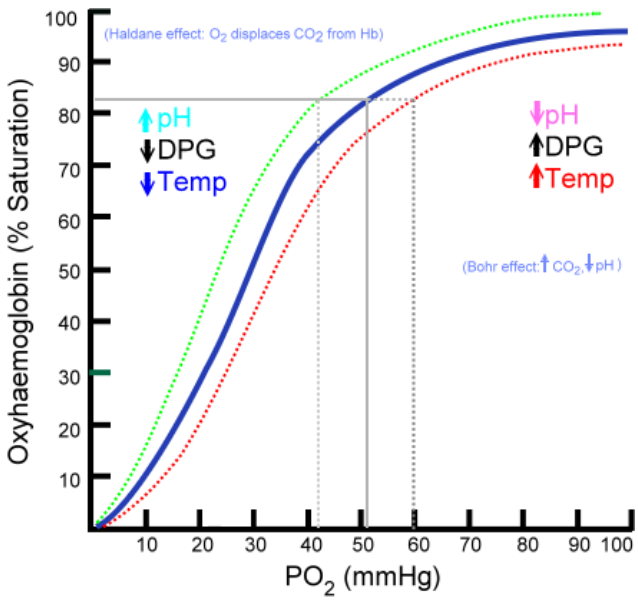
- Shifts to right = for given oxygen tension there is ↓ saturation of Hb with oxygen i.e. Enhanced oxygen delivery to tissues
- Shifts to left = for given oxygen tension there is ↑ saturation of Hb with oxygen i.e. ↓ oxygen delivery to tissues

Shifts to **R**ight = **R**aised oxygen delivery

- Raised [H^+] (acidity)
- Raised PCO_2
- Raised 2,3-DPG
- Raised temperature

Shifts to Left = Lower oxygen delivery

- HbF, methemoglobin, carboxyhemoglobin
- Low [H^+] (alkali)
- Low PCO_2
- Low 2,3-DPG
- Low temperature



Chloride shift

- CO_2 diffuses into RBCs
- $CO_2 + H_20$ ---- carbonic anhydrase → $HCO_3- + H^+$
- H^+ combines with Hb
- HCO_3- diffuses out of cell,- Cl^- replaces it

Bohr Effect

- Increasing acidity (or pCO_2) means O_2 binds less well to Hb → better tissue oxygenation.

Haldane Effect

- ↑ pO_2 means CO_2 binds less well to Hb → better CO_2 elimination.

Many factors influence the affinity of this binding and alter the shape of the curve:

	Right Shift	Left Shift
temperature	raised	low
2.3-DPG	raised	low
p(CO_2)	raised	low
p(CO)	low	raised
pH (Bohr effect)	low (raised acidosis)	raised (alkalosis)
type of hemoglobin	adult hemoglobin	fetal hemoglobin

Left shift of the curve is a sign of hemoglobin's ↑ affinity for oxygen (eg. at the lungs). Similarly, right shift shows ↓ affinity, as would appear with an ↑ in body temperature, hydrogen ion, 2,3-diphosphoglycerate (also known as bisphosphoglycerate) or carbon dioxide concentration (the Bohr effect)

Carbon monoxide has a much higher affinity for hemoglobin than oxygen does. In carbon monoxide poisoning, oxygen cannot be transported and released to body tissues thus resulting in hypoxia.

With fetal hemoglobin, the shift facilitates diffusion of oxygen across the placenta. The oxygen dissociation curve for myoglobin exists even further to the left.

Transfer factor

- **Raised: asthma, hemorrhage, left-to-right shunts, polycythemia**
- **Low: everything else**

Where alveolar hemorrhage occurs the TLCO tends to ↑ due to the enhanced uptake of carbon monoxide by intra-alveolar hemoglobin

Transfer factor

The transfer factor describes the rate at which a gas will diffuse from alveoli into blood. Carbon monoxide is used to test the rate of diffusion. Results may be given as the total gas transfer (TLCO) or that corrected for lung volume (transfer coefficient, KCO)

Causes of a raised TLCO	Causes of a lower TLCO
• Asthma • Pulmonary hemorrhage (wegener's, goodpasture's) • Left-to-right cardiac shunts • Polycythemia • Hyperkinetic states • ♂ gender, exercise	• Pulmonary fibrosis • Pneumonia • Pulmonary emboli • Pulmonary edema • Emphysema • Anemia • Low cardiac output

KCO also tends to ↑ with age (used to diagnose or R/O interstitial lung disease). Some conditions may cause ↑ KCO with a normal or ↓ TLCO

- Pneumonectomy/lobectomy
- Scoliosis/kyphosis
- Neuromuscular weakness
- Ankylosis of costovertebral joints e.g. Ankylosing spondylitis

Pulmonary arteries vasoconstrict in the presence of hypoxia

A fall in the partial pressure of oxygen (pO_2) in the blood leads to vasoconstriction of the pulmonary arteries. This allows blood to be divered to better aerated areas of the lung and improves the efficiency of gaseous exchange

Contraindications for Thoracentesis

An uncooperative patient or coagulation disorders that can not be corrected are absolute contraindications.

Relative contraindications include cases in which the site of insertion has known bullous disease (e.g. emphysema), use of positive end-expiratory pressure (PEEP, in mechanical ventilation) and only one functioning lung (due to diminished reserve). The aspiration should not exceed 1L as there is a risk of development of pulmonary edema.

Bronchial Asthma

Asthma diagnosis - if high probability of asthma - start treatment

The new British Thoracic Society guidelines take a more practical approach to diagnosing asthma. If a patient has typical symptoms of asthma a trial of treatment is recommended. Normal spirometry when the patient is well does not exclude a diagnosis of asthma.

The 2008 British Thoracic Society guidelines marked a subtle change in the approach to diagnosing asthma. It suggests dividing patients into a high, intermediate and low probability of having asthma based on the presence or absence of typical symptoms.

The following can cause Asthma:

- Isocyanates
- Platinum salts
- Soldering flux resin
- Glutaraldehyde
- Flour
- Epoxy resins
- Proteolytic enzymes

Diagnosis

- Specific recommendations are made in the 2007 joint British Thoracic Society and SIGN guidelines
- Serial measurements of peak expiratory flow are recommended at work and away from work
- Morning dip in PEFR >20%

Example of features used to assess asthma

↑ possibility of asthma	↓ possibility of asthma
• Wheeze, breathlessness, chest tightness and cough, worse at night/early morning • History of atopic disorder • Wheeze heard on auscultation • Unexplained peripheral blood eosinophilia	• Prominent dizziness, light-headedness, peripheral tingling • Chronic productive cough in the absence of wheeze or breathlessness • Repeatedly normal physical examination • Significant smoking history (i.e. > 20 pack-years) • Normal PEF or spirometry when symptomatic

Management is based on this assessment:

- High probability: trial of treatment
- Intermediate probability: see below
- Low probability: investigate/treat other condition

For patients with an intermediate probability of asthma further investigations are suggested. The guidelines state that spirometry is the preferred initial test:

- FEV1/FVC < 0.7: trial of treatment
- FEV1/FVC > 0.7: further investigation/consider referral

Recent studies have shown the limited value of other 'objective' tests. It is now recognised that in patients with normal or near-normal pre-treatment lung function there is little room for measurable improvement in FEV1 or peak flow.

A > 400 ml improvement in FEV1 is considered significant

- Before and after 400 mcg inhaled salbutamol in patients with diagnostic uncertainty and airflow obstruction present at the time of assessment
- If there is an incomplete response to inhaled salbutamol, after either inhaled corticosteroids (200 mcg twice daily beclomethasone equivalent for 6-8 weeks) or oral prednisolone (30 mg once daily for 14 days)

It is now advised to interpret **peak flow** variability with caution due to the **poor sensitivity** of the test

- Diurnal variation % = [(Highest – Lowest PEFR) / Highest PEFR] x 100
- Assessment should be made over 2 weeks
- Greater than 20% diurnal variation is considered significant

Stepwise management of stable asthma is now well established with a step-wise approach:

1	Inhaled short-acting β_2 agonist as required (e.g Sulbutamol PRN)
2	Add inhaled steroid at 200-800 mcg/day (beclometasone dipropionate or equivalent) 400 mcg is an appropriate starting dose for many patients. Start at dose of inhaled steroid appropriate to severity of disease
3	1. Add inhaled long-acting β_2 agonist (LABA) 2. Assess control of asthma: • Good response to LABA - continue LABA • Benefit from LABA but control still inadequate: continue LABA and ↑ inhaled steroid dose to 800 mcg/day* (if not already on this dose) • No response to LABA: stop LABA and ↑ inhaled steroid to 800 mcg/ day.* If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline
4	Consider trials of: • Increasing inhaled steroid up to 2000 mcg/day • Addition of a fourth drug e.g. Leukotriene receptor antagonist, SR theophylline, β_2 agonist tablet
5	Use daily steroid tablet in lowest dose providing adequate control. Consider other treatments to minimise the use of steroid tablets Maintain high dose inhaled steroid at 2000 mcg/day Refer patient for specialist care

Additional notes

Leukotriene Receptor Antagonists:

- E.g. Montelukast (causes Churg-Strauss syndrome), zafirlukast
- Have both anti-inflammatory and bronchodilatory properties
- Should be used when patients are poorly controlled on high-dose inhaled corticosteroids and a long-acting β_2 agonist
- Particularly useful in aspirin-induced asthma
- Associated with the development of churg-strauss syndrome

Fluticasone is more lipophilic and has a longer duration of action than beclometasone	**Hydrofluoroalkane** is now replacing chlorofluorocarbon as the propellant of choice. Only half the usually dose is needed with hydrofluoroalkane due to the smaller size of the particles	**Long acting β_2 agonists (LABA)** acts as bronchodilators but also inhibit mediator release from mast cells. Recent meta-analysis showed adding salmeterol improved symptoms compared to doubling the inhaled steroid dose

Patients with acute severe asthma are stratified into moderate, severe or life-threatening

Moderate	Severe	Life-threatening
• PEF > 50% best or predicted • Speech normal • RR < 25 / min • Pulse < 110 bpm	• PEF 33 - 50% best or predicted • Can't complete sentences • RR > 25/min • Pulse > 110 bpm	• PEF < 33% best or predicted • SpO_2 < 92% • Silent chest, cyanosis or feeble respiratory effort • Bradycardia, dysrhythmia or hypotension • Exhaustion, confusion or coma

British Thoracic Society guidelines 2003 (updated 2004)

- Magnesium sulphate recommended as next step for patients who are not responding (e.g. 1.2 - 2g IV over 20 mins)
- Little evidence to support use of IV aminophylline (although still mentioned in management plans)
- If no response consider IV salbutamol
- If the patient is developing respiratory acidosis (pH <7.35) consider intubation

COPD:

Causes:

- Smoking.
- Alpha-1 antitrypsin deficiency
- Cadmium (used in smelting)
- Coal
- Cotton
- Cement
- Grain

NICE (2010) recommend considering a diagnosis of COPD in patients over 35 years of age who are smokers or ex-smokers and have symptoms such as exertional breathlessness, chronic cough or regular sputum production. The following **investigations** are recommended in patients with suspected COPD:

- To demonstrate airflow obstruction: post-bronchodilator spirometry: FEV1/FVC < 70%
- Chest x-ray: hyperinflation, bullae, flat hemidiaphragm. Also important to exclude lung cancer
- Full blood count: exclude secondary polycythemia
- Body mass index (BMI) calculation

The severity of COPD is categorised using the FEV1:

Stage	Severity	FEV1 (of predicted)	Post-bronchodilator FEV1/FVC
I	Mild*	>80%	<0.7
II	Moderate	50–80%	
III	Severe	30–49%	
IV	Very Severe	< 30%	

(FEV1 is used for assessment of severity **NOT FOR DIAGNOSIS**). Measuring peak expiratory flow is of limited value in COPD, as it may underestimate the degree of airflow obstruction

* Grading system has changed following the 2010 NICE guidelines. If the FEV1 is greater than 80% predicted but the post-bronchodilator FEV1/FVC is < 0.7 then this is classified as Stage I – mild. Symptoms should be present to diagnose COPD in these patients

Chronic Management: NICE updated it's guidelines on the management of chronic obstructive pulmonary disease (COPD) in 2010.

General management

- Smoking cessation advice
- Annual influenza vaccination
- Pneumococcal vaccination

Bronchodilator therapy

- Short-acting β2-agoinst (SABA) or short-acting muscarinic antagonist (SAMA) is 1st line Rx.
- For patients who remain breathless or have exacerbations despite using short-acting bronchodilators the next step is determined by the FEV1

FEV1 > 50% (Stage I and II)	FEV1 < 50% (stage III and IV)
• Long-acting β2-agoinst (LABA), for example salmeterol, or: • Long-acting muscarinic antagonist (LAMA), for example tiotropium	• LABA + inhaled corticosteroid (ICS) in a combination inhaler, or: • LAMA

For patients with persistent exacerbations or breathlessness

- If taking a LABA then switch to a LABA + ICS combination inhaler
- Otherwise give a LAMA and a LABA + ICS combination inhaler

Oral theophylline

- NICE only recommends theophylline after trials of short and long-acting bronchodilators or to people who cannot use inhaled therapy
- The dose should be reduced if macrolide or fluroquinolone antibiotics are coprescribed

Mucolytics

- Should be 'considered' in patients with a chronic productive cough and continued if symptoms improve

Cor pulmonale

- Features include peripheral oedema, raised JVP, systolic parasternal heave, loud P_2
- Use a loop diuretic for oedema, consider long-term oxygen therapy
- ACE-inhibitors, calcium channel blockers and alpha blockers are **NOT** recommended by NICE

Factors which may improve survival in patients with stable COPD

- Smoking cessation - the single most important intervention in patients who are still smoking
- Long term oxygen therapy in patients who fit criteria
- Lung volume reduction surgery in selected patients

The 2010 NICE guidelines on COPD clearly define which patients should be assessed for and offered **long-term oxygen therapy (LTOT).** Patients who receive LTOT should breathe supplementary oxygen for at least 15 hours a day.

Assess patients if any of the following:

- Very severe airflow obstruction (FEV1 < 30% predicted). Assessment should be 'considered' for patients with severe airflow obstruction (FEV1 30-49% predicted)
- Cyanosis
- Polycythaemia
- Peripheral oedema
- Raised jugular venous pressure
- Oxygen saturations ≤ 92% on room air

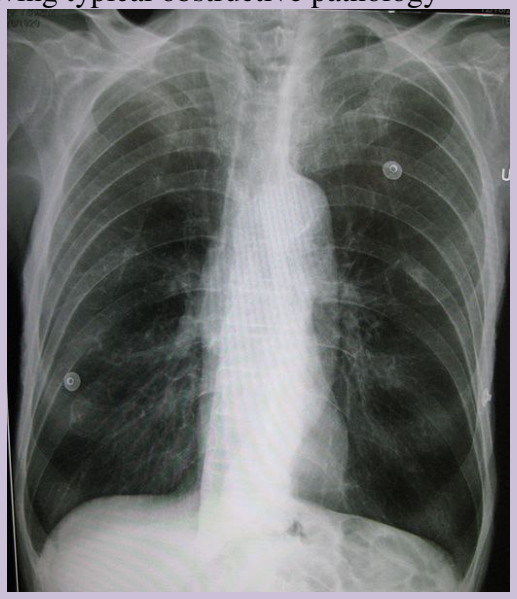
Assessment is done by measuring arterial blood gases on 2 occasions at least 3 weeks apart in patients with stable COPD on optimal management.

Offer LTOT to patients with a pO_2 of < 7.3 kPa or to those with a pO_2 of 7.3 - 8 kPa and one of the following:

- Secondary polycythaemia
- Nocturnal hypoxaemia
- Peripheral oedema

Emphysema is an irreversible degenerative condition; it is a known complication of COPD.

- ↑ Residual Volume (RV)
- ↑ Total Lung Capacity (TLC)
- Giving typical obstructive pathology



- Flattening of diaphragms: ↑ lung volumes
- Enlarged left pulmonary artery
- Attenuation of vessels
- Diffuse hyperlucency

Types:

- **Panacinar** (panlobular): entire respiratory acinus, from respiratory bronchiole to alveoli, is expanded. **> In the lower lobes.**
- **Centriacinar** (centrilobular): respiratory bronchiole (proximal and central part of the acinus) is expanded. The distal acinus or alveoli are unchanged. **> In the upper lobes.**
- Congenital lobar emphysema (CLE): results in overexpansion of a pulmonary lobe and resultant compression of the remaining lobes of the ipsilateral lung, and possibly contralateral lung. There is bronchial narrowing because of weakened or absent bronchial cartilage. There may be congenital extrinsic compression, commonly by an abnormally large pulmonary artery. CLE is potentially reversible, yet possibly life-threatening, causing respiratory distress in the neonate.
- Paraseptal emphysema: involves the alveolar ducts and sacs at the lung periphery. The emphysematous areas are subpleural in location and often surrounded by interlobular septa (hence the name). It may be an incidental

- Pulmonary hypertension

Benefits of LTOT:

- ↓ secondary polycythemia
- ↓ sympathetic activity → ↓ cardiac arrhythmia
- Improve sleep quality

finding in young adults, and may be associated with spontaneous pneumothorax. It may also be seen in older patients with centrilobular emphysema. Both centrilobular and paraseptal emphysema may progress to bullous emphysema.

Emphysematous Bulla is defined as being at least 1 cm in diameter, and with a wall less than 1mm thick. Bullae are thought to arise by air trapping in emphysematous spaces, causing local expansion

Oxygen Therapy:

The British Thoracic Society published guidelines on emergency oxygen therapy in 2008. The following selected points are taken from the guidelines.

Oxygen saturation targets

- Acutely ill patients: 94-98%
- Patients at risk of hypercapnia (e.g. COPD patients): 88-92% (see below)
- Oxygen should be ↓ in stable patients with satisfactory oxygen saturation

Management of COPD patients

- Prior to the availability of blood gases, use a 28% Venturi mask at 4 l/min and aim for an oxygen saturation of 88-92% for patients with risk factors for hypercapnia but no prior history of respiratory acidosis
- Adjust target range to 94-98% if the pCO_2 is normal

Situations where **oxygen therapy should not be used routinely** if there is no evidence of hypoxia:

- Myocardial infarction and acute coronary syndromes
- Stroke
- Obstetric emergencies
- Anxiety-related hyperventilation

Non-invasive ventilation:

the British Thoracic Society (BTS) published guidelines in 2002 on the use of non-invasive ventilation in acute respiratory failure

Non-invasive ventilation - key indications

- COPD with respiratory acidosis pH 7.25-7.35
- Type II respiratory failure secondary to chest wall deformity, neuromuscular disease or obstructive sleep apnoea
- Cardiogenic pulmonary edema unresponsive to CPAP
- Weaning from tracheal intubation.

Recommended initial settings for bi-level pressure support in COPD

- Expiratory Positive Airway Pressure (EPAP): 4-5 cm H_2O
- Inspiratory Positive Airway Pressure (IPAP): RCP advocate 10 cm H_20 whilst BTS suggest 12-15 cm H_2O
- FiO_2: not > 40%
- Back up rate: 15 breaths/min

- Back up inspiration:expiration ratio: 1:3
- Keep SpO_2: 88-92%
- ABG every 1-2 hours

Pulmonary Embolism (PE)

INVESTIGATION: The British Thoracic Society (BTS) published guidelines in 2003 on the investigation of patients with suspected pulmonary embolism (PE)

Key points from the guidelines include:

- Computed Tomographic Pulmonary Angiography (**CTPA**) is now the **recommended initial lung-imaging modality for non-massive PE**. Advantages compared to V/Q scans include speed, easier to perform out-of-hours, a ↓ need for further imaging and the possibility of providing an alternative diagnosis if PE is excluded
- If the CTPA is negative then patients do not need further investigations or treatment for PE
- Ventilation-Perfusion scanning **(V/Q) MAY BE USED INITIALLY IF** appropriate facilities exist, the chest x-ray is normal, and there is no significant symptomatic concurrent cardiopulmonary disease

Some other points:
Clinical probability scores based on risk factors and history and now widely used to help decide on further investigation/management

CXR:

- Could be normal

D-Dimers

- Sensitivity = 95-98%, but poor specificity (already high in pregnant women → useless)

V/Q scan

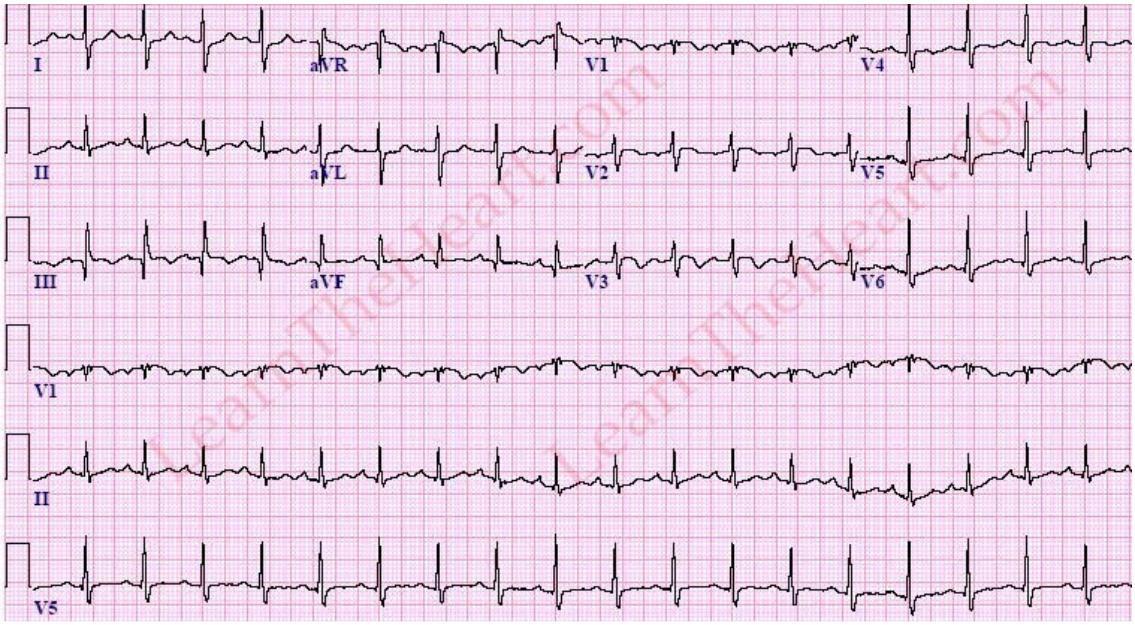
- Sensitivity = 98%; specificity = 40% - high negative predictive value, i.e. If normal virtually excludes PE
- Other causes of mismatch in V/Q include:
    - Old pulmonary embolisms
    - AV malformations
    - Vasculitis
    - Previous radiotherapy
- COPD gives matched defects

CTPA

- Peripheral emboli affecting subsegmental arteries may be missed

Pulmonary angiography

- The gold standard
- Significant complication rate compared to other investigations



ECG: $S_1Q_3T_3$

Unfortunately there is a lack of clear guidelines on the optimal length of anticoagulation following a pulmonary embolism. The 2003 British Thoracic Society guidelines which advocate a shorter duration of treatment are not widely followed. The following is based on the 2005 British Committee for Standards in Hematology (BCSH) guidelines and Clinical Knowledge Summaries.

Initial anticoagulation with heparin

- Low molecular weight heparin (LMWH), rather than unfractionated heparin (UFH), should be used routinely in patients with suspected pulmonary embolism. This reflects the equal efficacy and safety of LMWHs as well as their ease of use
- Exceptions include patients with a massive PE or in situations where rapid reversal of anticoagulation may be necessary

Massive PE + hypotension → thrombolyse

Ongoing anticoagulation with warfarin (Target INR 2 – 3) length of treatment:

- Calf DVT: at least 6 weeks
- Proximal DVT or PE where there is **transient risk factors**: at least **3 months**
- **Idiopathic** venous thromboembolism or **permanent risk factors**: at least **6 months**

Thrombolysis

- Thrombolysis is now recommended as the first-line treatment for massive PE where there is circulatory failure (e.g. Hypotension). Other invasive approaches should be considered where appropriate facilities exist

Community Acquired Pneumonia (CAP) may be caused by the following organisms:

- *Streptococcus pneumoniae* (accounts for around 80% of cases)
- *Hemophilus influenzae*
- *Staphylococcal aureus*
- Atypical pneumonias (e.g. due to *Mycoplasma pneumoniae*)
- Viruses

Streptococcus pneumoniae commonly causes reactivation of the herpes simplex virus resulting in 'cold sores and associated with foreign travel

Klebsiella pneumoniae (Friedlander's pneumonia) is classically in alcoholics. CXR features may include **abscess formation** in the middle/upper lobes and empyema. The mortality approaches 30-50%

Staphylococcus aureus: normally causes pneumonia **only AFTER a preceding influenzal viral infection**. Characteristically causes **multiple abscesses** in up to 25% of patients and empyema in 10%, septicemia develops with metastatic abscess in other organs such as brain and bones.

Characteristic features of pneumococcal pneumonia

- Rapid onset
- High fever
- Pleuritic chest pain
- Herpes labialis

Antibiotic choices The British Thoracic Society published guidelines in 2009:

- Low or moderate severity CAP: oral amoxicillin. A macrolide should be added for patients admited to hospital
- High severity CAP: intravenous co-amoxiclav + clarithromycin OR cefuroxime + clarithromycin OR cefotaxime + clarithromycin

Pneumonia Prognostic Factors:

CURB-65 criteria of severe pneumonia

- Confusion (abbreviated mental test score < 8/10)
- Urea > 7 mmol/L
- Respiratory rate = 30 / min
- BP: systolic < 90 or diastolic < 60 mmHg
- age > 65 years

Patients with 3 or more (out of 5) of the above criteria are regarded as having a severe pneumonia

Other factors associated with a poor prognosis include:

- Presence of coexisting disease
- Hypoxemia (pO_2 < 8 kPa) independent of FiO_2

Streptococcus Pneumoniae (pneumococcus) is the most common cause of CAP

Bacterial organisms that cause infective exacerbations of COPD

- *Hemophilus influenzae* (most common cause)
- *Streptococcus pneumoniae*
- *Moraxella catarrhalis*

Respiratory viruses account for around 30% of exacerbations, with the human rhinovirus being # 1.

Mycoplasma pneumoniae is a cause of atypical pneumonia which often affects younger patients frequently amongst those living in boarding houses (housings, hostels). It is associated with a number of **characteristic complications such as erythema multiforme (target lesion)** and cold autoimmune hemolytic anemia **(*pneumococcus* may also cause erythema multiforme)**. Epidemics of *Mycoplasma pneumoniae* classically occur every 4 years. It is important to recognise atypical pneumonias as they may not respond to penicillins or cephalosporins.

Features

- Flu-like symptoms classically **PRECEDE** a dry cough
- Bilateral consolidation on x-ray
- Complications:
  - Cold agglutins (IgM) may cause an hemolytic anemia, thrombocytopenia
  - Erythema multiforme, erythema nodosum
  - Meningoencephalitis, Guillain-Barre syndrome
  - Bullous myringitis: painful vesicles on the tympanic membrane
  - Pericarditis/myocarditis
  - Gastrointestinal: hepatitis, pancreatitis
  - Renal: acute glomerulonephritis

Diagnosis

- Mycoplasma serology
- Can be differentiated from other types of pneumonia by the relatively slow progression of symptoms, a positive coombs in 50-70% after 10 days of infection (should be used with caution or not at all since 50% of the tests are false-positive), lack of bacteria in a gram-stained sputum, and a lack of growth on blood agar.
- PCR has also been used

Management

- Erythromycin/clarithromycin
- Tetracyclines such as doxycycline are an alternative

***Pneumocystis carinii* pneumonia (PCP):** whilst the organism *Pneumocystis carinii* is now referred to as *Pneumocystis jiroveci*, the term *Pneumocystis carinii* pneumonia (PCP) is still in common use

- *Pneumocystis jiroveci* is an unicellular eukaryote, generally classified as a fungus but some authorities consider it a protozoa
- **PCP is the most common opportunistic infection in AIDS**
- All patients with a CD4 count < 200/mm³ should receive PCP prophylaxis

Features

- Dyspnea
- Dry cough
- Fever
- Very few chest signs

- Young Patient
- Signs & Symptoms of chest infection
- Hematuria

Mycoplasma Pneumonia

Extrapulmonary manifestations are **rare** (1-2% of cases), may cause

- Hepatosplenomegaly
- Lymphadenopathy
- Choroid lesions

Investigation

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal
- Exercise-induced desaturation
- Sputum often fails to show PCP, bronchoalveolar lavage (BAL) often needed to demonstrate PCP (silver stain)

Management

- Co-trimoxazole
- IV pentamidine in severe cases
- Steroids if hypoxic (if pO_2 < 9.3kPa (9.3*7.5=71mmHg) then steroids ↓ risk of respiratory failure by 50% and death by a third)

Legionella pneumonia or Legionnaire's disease is caused by the intracellular bacterium *Legionella pneumophilia (Gram –ve bacilli)*. It is typically colonizes water tanks (hint → **air-conditioning systems, showers or foreign holidays**) Person-to-person transmission is not seen

Features

- Flu-like symptoms
- 50% of cases have GI symptoms such as nausea, vomiting, diahrrhea and abdominal pain.
- Dry cough
- Lymphopenia
- Hyponatremia
- Deranged LFTs
- Hematuria occurs and occasionally renal failure.

Legionella is suggested if 3 of the following 4 features are present:

- Prodormal viral like illness
- Dry cough, confusion or diarrhea
- Lymphopenia without marked leukocytosis.
- Hyponatremia

Diagnosis

- Urinary antigen

Management

- Treat with erythromycin

Extrinsic Allergic Alveolitis (EAA) is a condition caused by hypersensitivity induced lung damage due to a variety of inhaled organic particles. It is thought to be largely caused by immune-complex mediated tissue damage (type **III hypersensitivity = acute phase**) although delayed hypersensitivity (type **IV = chronic phase**) is also thought to play a role in EAA, especially in the chronic phase

Examples

- Bird fanciers' lung (avian proteins)
- Farmers lung (spores of micropolyspora faeni)
- Malt workers' lung (aspergillus clavatus)
- Mushroom workers' lung (thermophilic actinomycetes*)

Presentation

- Acute: occur 4-8 hrs after exposure, SOB, dry cough, fever
- Chronic

NOT ALLERGY:

- No eosinophilia
- No ↑ IgE
- No positive skin prick

Investigation

- CXR: upper lobe fibrosis
- BAL (bronchoalveolar lavage): lymphocytosis
- **Blood: NO eosinophilia**
- Circulating IgG precipitant

*here the terminology is slightly confusing as thermophilic actinomycetes is an umbrella term covering strains such as Micropolyspora faeni

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Lung Fibrosis: it is important in the exam to be able to differentiate between conditions causing predominately upper or lower zone fibrosis. It should be noted that the more common causes (cryptogenic fibrosing alveolitis, drugs) tend to affect the lower zones

Fibrosis predominately affecting the **UPPER ZONES**

- Extrinsic allergic alveolitis
- Coal worker's pneumoconiosis/progressive massive fibrosis
- Silicosis
- Sarcoidosis
- Ankylosing spondylitis (rare)
- Histiocytosis
- Tuberculosis

Fibrosis predominately affecting the **LOWER ZONES**

- Cryptogenic fibrosing alveolitis
- Most connective tissue disorders (except ankylosing spondylitis)
- Drug-induced: amiodarone, bleomycin, methotrexate
- Asbestosis

Asbestosis: the severity of asbestosis is related to the length of exposure. This is in contrast to mesothelioma where even very limited exposure can cause disease. The latent period is typically 15-30 years. Asbestosis typically causes lower lobe fibrosis. As with other forms of lung fibrosis the most common symptoms are shortness-of-breath and reduced exercise tolerance. Crocidolite (blue) asbestos is the most dangerous form

Possible features

- Progressive SOB
- Chest pain
- Pleural effusion

Mesothelioma:

- Smoking does not ↑ risk of mesothelioma
- Exposure to radiation ↑ the risk

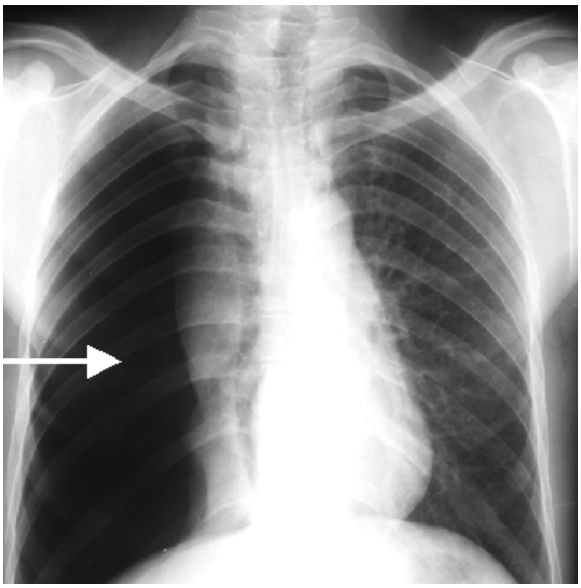
Other features

- Pleural thickening in a similar pattern to that seen following an empyema or hemothorax. The underlying pathophysiology is not fully understood.
- Pleural plaques also seen (not premalignant). They are the most common form of asbestos related lung disease and generally occur after a latent period of 20-40 years.

Patients are usually offered palliative chemotherapy and there is also a limited role for surgery and radiotherapy. Unfortunately the prognosis is very poor, with a median survival from diagnosis of 8-14 months.

Lung Cancer:
Asbestos exposure is a risk factor for lung cancer and also has a synergistic effect with cigarette smoke (this is true for lung ca not for mesothelioma).

Pneumothorax: The British Thoracic Society (BTS) published guidelines for the management of spontaneous pneumothorax in 2003. A pneumothorax is termed primary if there is no underlying lung disease and secondary if there is. Pt cannot air-travel for 2 weeks post complete aspiration of the air.



Primary pneumothorax:

- If the rim of air is < 2cm and the patient is not short of breath then discharge should be considered
- Otherwise aspiration should be attempted
- If this fails then repeat aspiration should be considered
- If this fails then a chest drain should be inserted

If patient is asthmatic → treat as secondary pneumothorax

Secondary pneumothorax:

- If the patient is > 50 years old and the rim of air is > 2cm and the patient is short of breath then a chest drain should be inserted.
- Otherwise aspiration should be attempted. If aspiration fails a chest drain should be inserted. All patients should be admitted for at least 24 hours

Iatrogenic pneumothorax:

- Less likelihood of recurrence than spontaneous pneumothorax
- Majority will resolve with observation, if treatment is required then aspiration should be used
- Ventilated patients need chest drains, as may some patients with COPD

Lung cancer:

Risk Factors:

Smoking

- ↑ risk of lung ca by a factor of 10

Factors that are NOT related

- **Coal dust**

Other factors

- Asbestos - ↑ risk of lung ca by a factor of 5
- Arsenic
- Radon
- Nickel
- Chromate
- Aromatic hydrocarbon
- Cryptogenic fibrosing alveolitis

Smoking +asbestos are synergistic, i.e. a smoker with asbestos exposure has a 10 x 5 = 50 times ↑ risk

Whilst many chemicals have been implicated in the development of lung cancer passive smoking is the most likely cause. Up to 15% of lung cancers in patients who do not smoke are thought to be caused by passive smoking

Referral:

The 2005 NICE cancer referral guidelines gave the following advice:
Consider immediate referral for patients with:

- Signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure)
- Stridor

Refer urgently patients with:

- Persistent hemoptysis (in smokers or ex-smokers aged 40 years and older)
- A chest x-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation)
- A normal chest x-ray where there is a high suspicion of lung cancer
- A history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms where a chest x-ray indicates pleural effusion, pleural mass or any suspicious lung pathology

Refer urgently for chest x-ray for patients with any of the following:

- Hemoptysis
- Unexplained or persistent (longer than 3 weeks): chest and/or shoulder pain, dyspnea, weight loss, chest signs, hoarseness, finger clubbing, cervical or supraclavicular lymphadenopathy, cough, features suggestive of metastasis from a lung cancer (for example, secondaries in the brain, bone, liver, skin)

- Underlying chronic respiratory problems with unexplained changes in existing symptoms

Types of lung cancer

- Squamous: 35%
- Adenocarcinoma: 30%
- Small (oat) cell: 15%
- Large cell: 10%
- Other: 5%

Squamous is the most common in UK, Adenocarcinoma is the most common in US

Other tumours

- Alveolar cell carcinoma: not related to smoking, ++sputum
- Bronchial adenoma: mostly carcinoid

Small Cell Lung Cancer:

Paraneoplastic features of lung cancer

- Squamous cell: PTHrp, clubbing, HPOA
- Small cell: ADH, ACTH, Lambert-Eaton syndrome

Features

- Usually central
- Arise from APUD* cells
- ADH → Hyponatremia
- ACTH → cushing's syndrome
- ACTH secretion can cause bilateral adrenal hyperplasia, the high levels of cortisol can lead to hypokalaemic alkalosis
- Lambert-eaton syndrome: antibodies to voltage gated calcium channels causing myasthenic like syndrome

Management

- Usually metastatic disease by time of diagnosis
- Surgery: only used for debulking
- Radiotherapy: only used for debulking
- Chemotherapy (being the **mainstay** of treatment): good response to combination chemotherapy, may extend life by approximately 4 months

***an acronym for**

- Amine - high amine content
- Precursor Uptake - high uptake of amine precursors
- Decarboxylase - high content of the enzyme decarboxylase

Contraindications to lung cancer surgery include SVC obstruction, FEV < 1.5, MALIGNANT pleural effusion, and vocal cord paralysis

Vocal Cord Paralysis → extracapsular spread to mediastinal nodes and is an indication of inoperability.

Non-Small Cell Management

There are three main subtypes of non-small cell lung cancer:

1. Squamous cell cancer

- Typically central
- Associated with ectopic PTH secretion → **HYPERCALCAEMIA**
- Strongly associated with finger clubbing
- Hypertrophic pulmonary osteoarthropathy (HPOA)

2. Adenocarcinoma

- Most common type of lung cancer in non-smokers, although the majority of patients who develop lung adenocarcinoma are smokers
- Typically located on the lung periphery

3. Large cell lung carcinoma

Management

- Only 20% suitable for surgery
- Mediastinoscopy prior to surgery as CT does not always show mediastinal node involvement
- Curative or palliative radiotherapy
- Poor response to chemotherapy

Surgery contraindications

- Assess general health
- Stage IIIb or IV (i.e. Metastases present)
- FEV1 < 1.5 litres is considered a general cut-off point*
- Malignant pleural effusion
- Tumour near hilum or within 2 cm of bronchus
- Vocal cord paralysis
- SVC obstruction

* However if FEV1 < 1.5 for lobectomy or < 2.0 for pneumonectomy then some authorities advocate further lung function tests as operations may still go ahead based on the results

Lung cancer: paraneoplastic features:

Small Cell

- ADH
- ACTH - not typical, hypertension, hyperglycemia, Hypokalemia, alkalosis and muscle weakness are more common than buffalo hump etc
- Lambert-Eaton syndrome

Squamous Cell

- PTH-rP
- Clubbing
- Hypertrophic pulmonary osteoarthropathy (HPOA)
- Hyperthyroidism due to ectopic TSH

Adenocarcinoma

- Gynaecomastia

Bronchial Carcinoma: 20-30% of cases with bronchial carcinoma are of the small (oat) cell type and arise from endocrine (Kulchitsky) cells.

Primary Bronchial Cancer, the tumor edge may have a fluffy or spiked appearance

Paraneoplastic manifestations:

- Syndrome of inappropriate ADH secretion (SIADH) 5-10%
- Ectopic secretion of ACTH 5%
- Ectopic atrial natriuretic peptide (ANP) secretion can also occur

Rheumatoid and Respiratory System

A variety of respiratory problems may be seen in patients with rheumatoid arthritis:

- Pulmonary fibrosis
- Pleural effusion
- Pulmonary nodules
- Bronchiolitis obliterans
- Complications of drug therapy e.g. Methotrexate pneumonitis
- Pleurisy
- Caplan's syndrome - massive fibrotic nodules with occupational coal dust exposure
- Infection (possibly atypical) secondary to immunosuppression

CXR Cavitations:

Differential

- Tuberculosis
- Lung cancer (especially squamous cell)
- Abscess (staph aureus, klebsiella and *Pseudomonas*)
- Wegener's granulomatosis
- Pulmonary embolism
- Rheumatoid arthritis
- Aspergillosis, histoplasmosis, coccidioidomycosis

Sarcoidosis CXR

- 0 = normal
- 1 = BHL
- 2 = BHL + infiltrates
- 3 = infiltrates
- 4 = fibrosis

Sarcoidosis: is a multisystem disorder of unknown aetiology characterized by non-caseating granulomas. It is more common in young adults and in people of African descent. **Sarcoidosis remits without treatment in approximately two-thirds of people.**

There is no one diagnostic test for sarcoidosis and hence diagnosis is still largely clinical. **ACE** levels have a sensitivity of 60% and specificity of 70% and are therefore not reliable in the diagnosis of sarcoidosis although they may have a role in **monitoring disease activity**. Routine bloods may show hypercalcemia (seen in 10% if patients) and a raised ESR

Other investigations*

- Spirometry: may show a restrictive defect
- Tissue biopsy: non-caseating granulomas
- Gallium-67 scan - not used routinely

*the Kveim test (where part of the spleen from a patient with known sarcoidosis is injected under the skin) is no longer performed due to concerns about cross-infection

Erythema nodosum is associated with a good prognosis in sarcoidosis

Prognostic Features:
Factors associated with **poor prognosis**

- Insidious onset, symptoms > 6 months
- Absence of erythema nodosum
- Extrapulmonary manifestations: e.g. Lupus pernio, splenomegaly
- CXR: stage III-IV features
- Black people

Mikulicz syndrome: is a chronic condition characterized by the abnormal enlargement of parotids, lacrimal and salivary glands. The tonsils and other glands in the soft tissue of the face and neck may also be involved. It is associated with sarcoidosis

Indications for steroids

- Hypercalcemia
- Worsening lung function
- Eye (bilateral posterior uveitis is common eye manifestation)
- Heart or neuro involvement

BHL: = (bulky mediastinum), the most common causes of Bilateral Hilar Lymphadenopathy are sarcoidosis and tuberculosis
Causes include:

- **Sarcoidosis**
- **Tuberculosis**
- Lymphoma/other malignancy
- Pneumoconiosis e.g. Berylliosis
- Fungi e.g. Histoplasmosis, coccidioidomycosis (VHL + Cavitation in CXR)

Lofgren's syndrome is an acute form sarcoidosis characterized by bilateral hilar lymphadenopathy (**BHL**), erythema nodosum, fever and polyarthralgia. It typically occurs in young ♀s and carries an excellent prognosis

- Transient CXR shadowing and blood eosinophilia
- Thought to be due to parasites such as Ascaris lumbricoides causing an alveolar reaction
- Presents with a fever, cough and night sweats which often last for less than 2 weeks.
- Generally a self-limiting disease

Causes of pulmonary Eosinophilia

- Churg-Strauss syndrome (eosinophilia + asthma + hemorrhage)
- Allergic bronchopulmonary aspergillosis (ABPA)
- Loffler's syndrome
- Eosinophilic pneumonia
- Hypereosinophilic syndrome
- Tropical pulmonary eosinophilia
- Drugs: nitrofurantoin, sulphonamides
- Less common: Wegener's granulomatosis
- Tropical pulmonary eosinophilia
- Associated with Wuchereria bancrofti infection

Occupational and Exposural Causes of Respiratory Diseases:

COPD Causes:

- Smoking!
- α-1 antitrypsin deficiency
- Cadmium (used in smelting)
- Coal
- Cotton
- Cement
- Grain

Diagnosis of occupational Asthma:

- Serial measurements of peak expiratory flow are recommended at work and away from work

Asthma Causes:

- Isocyanates
- Platinum salts
- Soldering flux resin
- Glutaraldehyde
- Flour
- Epoxy resins
- Proteolytic enzymes

Silicosis is a risk factor for developing TB (silica is toxic to macrophages)
Features

- Fibrosing lung disease
- 'Egg-shell' calcification of hilar lymph nodes

Respiratory Alkalosis

Common causes

- Anxiety leading to hyperventilation
- Pulmonary embolism
- Salicylate poisoning*
- CNS disorders: stroke, subarachnoid hemorrhage, encephalitis
- Altitude
- Pregnancy

*salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis. Early stimulation of the respiratory centre leads to a respiratory alkalosis whilst later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis

Bronchiectasis describes a permanent dilatation of the airways secondary to chronic infection or inflammation. There are a wide variety of causes are listed below:

Causes

- Post-infective: tuberculosis, measles, pertussis, pneumonia
- Cystic fibrosis
- Bronchial obstruction e.g. Lung cancer/foreign body
- Immune deficiency: selective IgA, hypogammaglobulinemia
- Allergic bronchopulmonary aspergillosis (ABPA)
- Ciliary dyskinetic syndromes: kartagener's syndrome, young's syndrome
- Yellow nail syndrome (associated with pleural effusion - exudates)

Symptom control in non-CF bronchiectasis - inspiratory muscle training + postural drainage

After assessing for treatable causes (e.g. immune deficiency) **MANAGEMENT** is as follows:

- Physical training (e.g. Inspiratory muscle training) - has a good evidence base for patients with non-cystic fibrosis bronchiectasis
- Postural drainage
- IV antibiotics for exacerbations + long-term rotating antibiotics (nebulized ABX) in severe cases
- Bronchodilators in selected cases
- Immunisations
- Surgery in selected cases (e.g. Localised disease)

Pseudomonas aeruginosa:

- Insensitive for Amoxicillin
- IV Ticarcillin + IV Gentamycin
- IV Colistin for resistant cases

Most common **organisms** isolated from patients with bronchiectasis:

- *Hemophilus influenzae* (most common)
- *Pseudomonas aeruginosa*
- Klebsiella spp.
- *Streptococcus pneumoniae*

Obstructive Sleep Apnoea/Hypopnoea Syndrome:

Predisposing factors

- Obesity
- Macroglossia: acromegaly, hypothyroidism, amyloidosis
- Large tonsils
- Marfan's syndrome

Consequence

- Daytime somnolence
- Hypertension

SIGN guidelines for the diagnosis and management of patients with OSAHS were published in 2003

Assessment of sleepiness

- Epworth Sleepiness Scale - questionnaire completed by patient +/- partner
- Multiple Sleep Latency Test (MSLT) - measures the time to fall asleep in a dark room (using EEG criteria)

Diagnostic tests

- Sleep studies - ranging from monitoring of pulse oximetry at night to full polysomnography where a wide variety of physiological factors are measured including EEG, respiratory airflow, thoraco-abdominal movement, snoring and pulse oximetry

Management

- Weight loss
- CPAP is first line for moderate or severe OSAHS
- Intra-oral devices (e.g. Mandibular advancement) may be used if CPAP is not tolerated or for patients with mild OSAHS where there is no daytime sleepiness
- Limited evidence to support use of pharmacological agents

Acute Respiratory Distress Syndrome - ARDS

Basics

- Caused by ↑ permeability of alveolar capillaries leading to fluid accumulation in alveoli i.e. Non-cardiogenic pulmonary edema

Criteria (American-European Consensus Conference)

- Acute onset
- Bilateral infiltrates on CXR
- Non-cardiogenic (pulmonary artery wedge pressure needed if doubt)
- $pO_2/FiO_2 < 200$ mmHg

Causes

- Infection: sepsis, pneumonia
- Massive blood transfusion
- Trauma
- Smoke inhalation
- Pancreatitis
- Cardio-pulmonary bypass

Allergic bronchopulmonary aspergillosis (ABPA) results from an allergy to Aspergillus spores. In the exam questions often give a history of bronchiectasis and eosinophilia.

Features

- Bronchoconstriction: wheeze, cough, dyspnea
- Bronchiectasis (proximal)

Investigations

- Eosinophilia
- Flitting CXR changes
- Positive radioallergosorbent (RAST) test to aspergillus

- Positive IgG precipitins (not as positive as in aspergilloma)
- Raised IgE

Management

- Steroids (think.. allergy to aspergillus)
- Itraconazole is sometimes introduced as a second line agent

---

Aspergilloma is a fungus ball which often colonises an existing lung cavity (e.g. secondary to TB, lung cancer or cystic fibrosis)

Usually asymptomatic but features may include

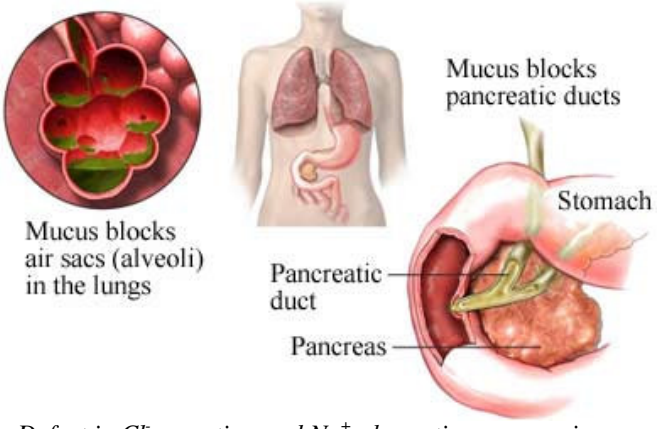
- Cough
- Hemoptysis (may be severe)

Investigations

- CXR containing a rounded opacity
- High titres Aspergillus precipitins

Cystic fibrosis (CF) is an autosomal recessive disorder causing ↑ viscosity of secretions (e.g. lungs and pancreas). It is due to a defect in the cystic fibrosis transmembrane conductance regulator gene (CFTR), which codes a cAMP-regulated chloride channel. **The most common inherited lethal condition in Caucasians**

In the UK 80% of CF cases are due to a deletion at delta F508 on the **long arm of chromosome 7**. Cystic fibrosis affects 1 per 2500 births, and the carrier rate is c. 1 in 25



Defect in Cl^- secretion and Na^+ absorption across airway epithelium

Organisms which may colonise CF patients

- Staph aureus
- *Pseudomonas aeruginosa* (Rx: Inhaled Tobramycin)
- Burkholderia cepacia*
- Aspergillus

Cyctic Fibrosis
Long list of problems
↓
Long arm of chromosome 7

***Cepacia* Syndrome in CF:** characterized by a rapidly progressive fever, uncontrolled bronchopneumonia, septicemia, weight loss, and poor outcomes.

Management:

- Aminoglycosides + Ceftazidime
- Ceftazidime + Cholramphenicol
- Cholramphenicol + Minocycline

*previously known as *Pseudomonas* cepacia

Presenting features

- Neonatal period (around 20%): meconium ileus, less commonly prolonged jaundice
- Recurrent chest infections (40%)
- GI Manifestation: malabsorption (30%) steatorrhoea, liver disease, cholesterol gall stones, peptic ulcers, ↑ GI malignancy.
- Other features: failure to thrive.

Diagnosis:

- Sweat test: 2 reliable positive results on 2 separate days is diagnostic for CF. it is positive when chloride is > 60

Other features of cystic fibrosis

- Short stature
- Diabetes Mellitus
- Delayed puberty
- Rectal prolapse (due to bulky stools)
- Nasal polyps
- ♂ infertility, ♀ subfertility

Management of cystic fibrosis involves a multidisciplinary approach. Key points:

- Regular (at least twice daily) chest physiotherapy and postural drainage. Parents are usually taught to do this. Deep breathing exercises are also useful
- High calorie diet, including high fat intake*
- Vitamin supplementation
- Pancreatic enzyme supplements taken with meals
- Heart and lung transplant

*this is now the standard recommendation - previously high calorie, low-fat diets have been recommended to ↓ the amount of steatorrhoea

Bronchiolitis obliterans:

is the term used to describe fibrous scarring of the small airways. It is seen following: toxic-fume inhalation; mineral-dust exposure; viral infection; mycoplasma and legionella infection; bone marrow, heart–lung and lung transplantation; rheumatoid arthritis; SLE; and as a side-effect of penicillamine. It presents as a dry cough and dyspnea. Physical examination is unremarkable. Expiratory wheeze may be audible. The chest X-ray findings can vary from normal to a reticular or reticulonodular pattern. The diagnosis can be confirmed by lung biopsy. Patients rarely respond to steroids. The prognosis is poor

Pleural Effusion:

Exudate - (> 30g/L protein)

- Infection: pneumonia, TB, subphrenic abscess
- Connective tissue disease: RA (glucose < 1.6, LDH > 700, pH < 7.2,↑ R.F > 1:320, ↑ cholesterol), SLE
- Neoplasia: lung cancer, mesothelioma, metastases
- Pancreatitis
- Pulmonary embolism
- Dressler's syndrome
- Yellow nail syndrome (also known as "Primary lymphedema associated with yellow dystrophic nails and pleural effusion. Approximately 40% will also have bronchiectasis. It is also associated with chronic sinusitis and persistent coughing. It usually affects adults and it's very rare)

Transudate - (< 30g/L protein)

- Heart failure
- Hypoalbuminemia (liver disease, nephrotic syndrome, malabsorption)
- Hypothyroidism
- Meigs' syndrome: triad of ascites, pleural effusion (right side) and benign ovarian tumor (fibroma). It resolves after the resection of the tumor. For reasons unknown.

Indications for chest tube insertion in patients with infected pleural effusions are: presence of organisms on a Gram stain of the pleural fluid, a frankly purulent pleural fluid, pleural pH < 7.2 in the setting of an infected pleural effusion, loculated pleural effusions and poor clinical progress despite antibiotic treatment.

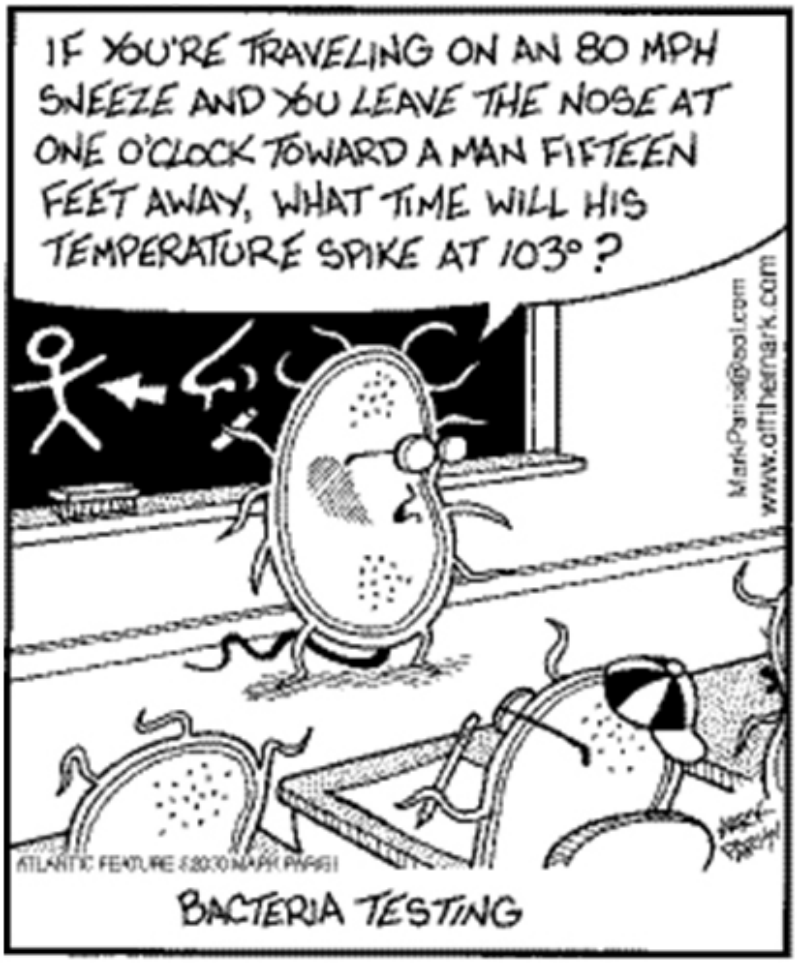
Transfusion Related Acute Lung Injury (TRALI): caused by anti-HLA, Human Neutrophil Antigens (HNA) or antigranulocytes antibody in donor blood.

Donor's blood sensitization occurs in:

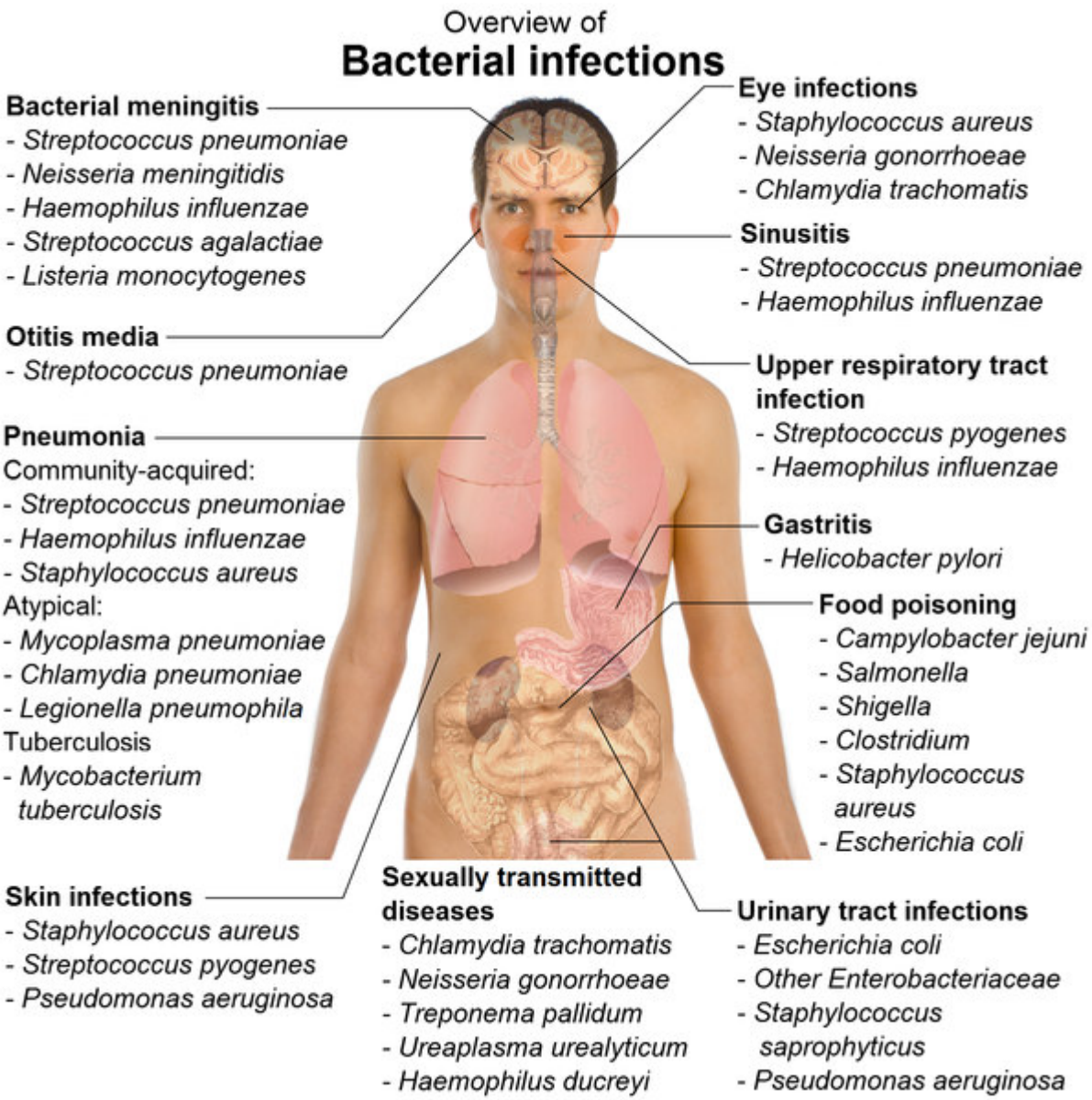
- Multiparous ♀ develop these antibodies through exposure to fetal blood
- Previous transfusion
- Transplantation patient

When blood is obtained from above mentioned donors, it carries higher risk for recipient to develop TRALI; those who have lung pathology are more susceptible. TRALI symptoms resemble ARDS.

Diagnosis: confirmed by finding of anti-HLA or anti-Neutrophil antibody in donors' or recipient blood.


IF YOU'RE TRAVELING ON AN 80 MPH SNEEZE AND YOU LEAVE THE NOSE AT ONE O'CLOCK TOWARD A MAN FIFTEEN FEET AWAY, WHAT TIME WILL HIS TEMPERATURE SPIKE AT 103°?
MarkParisi@aol.com
www.offthemark.com
BACTERIA TESTING

INFECTIOUS AND STD DISEASES



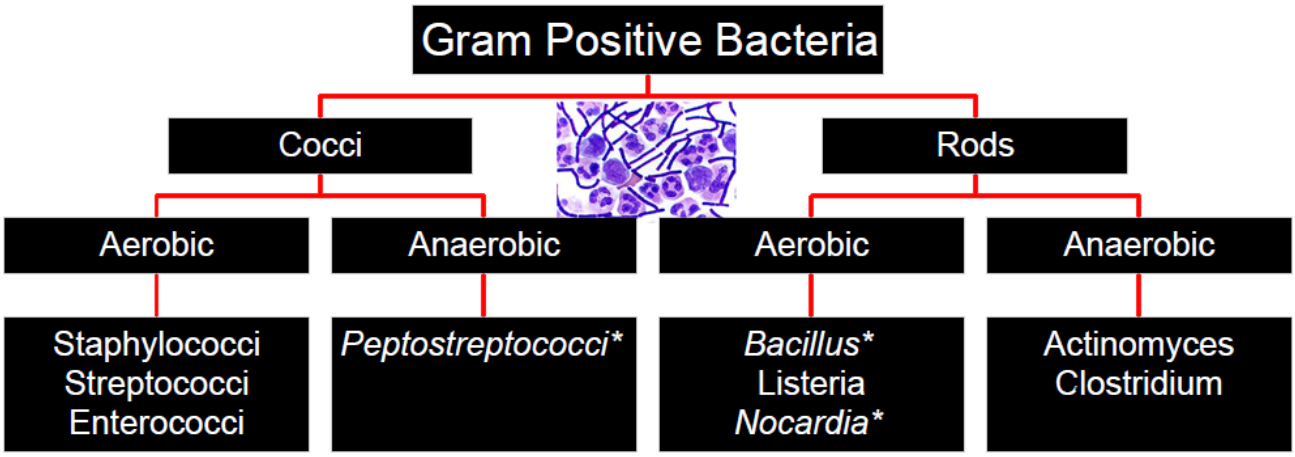
BACTERIAL CLASSIFICATION

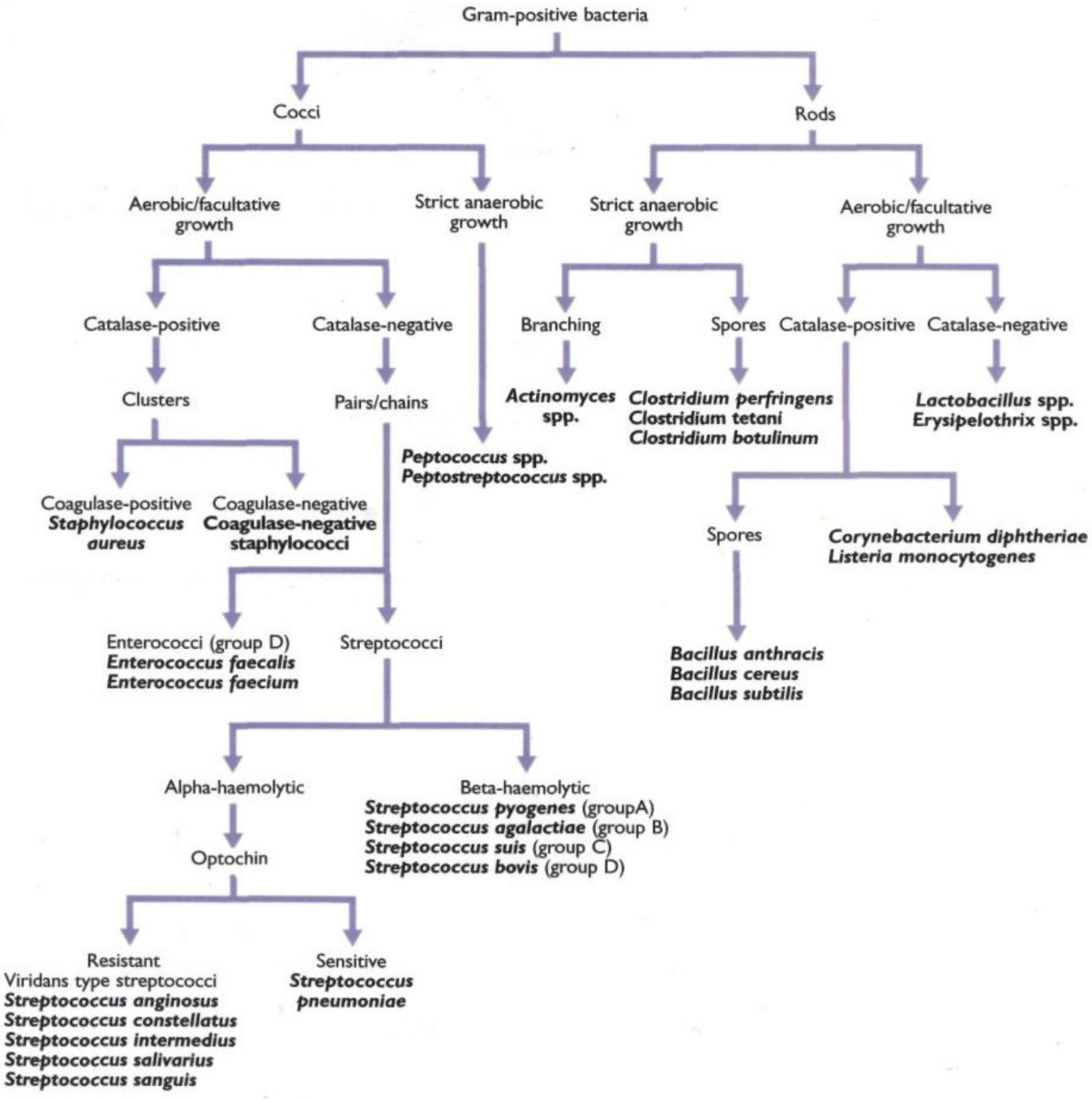
- Gram **P**ositive cocci = sta**P**hylococci + stre**P**tococci (including enterococci)
- Gram **N**egative cocci = ***N****eisseria meningitidis* + ***N****eisseria gonorrhoeae*, also ***Moraxella***

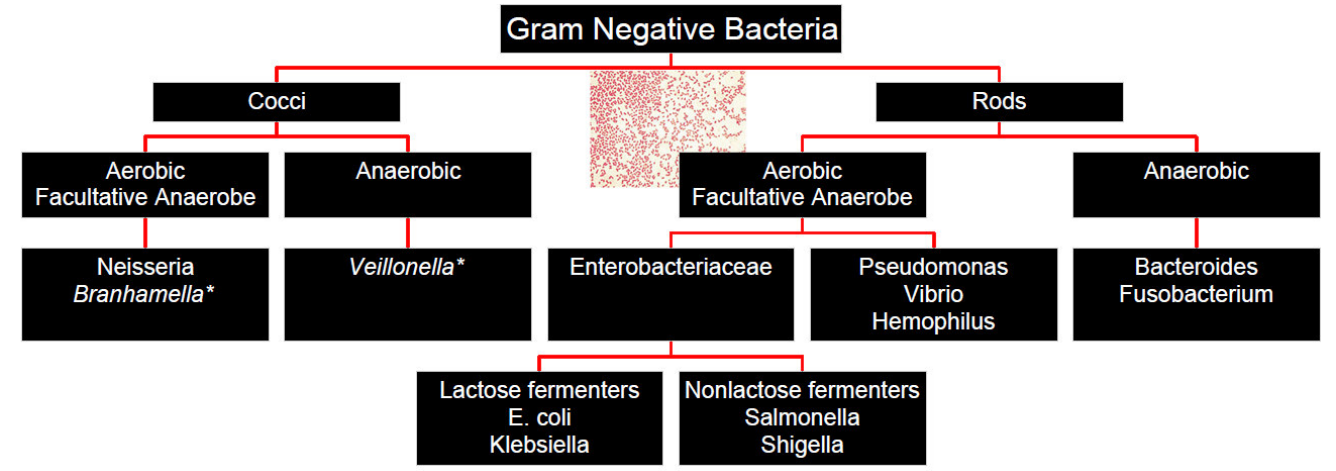
Therefore, only a small list of Gram positive rods (bacilli) need to be memorised to categorise all bacteria - mnemonic = ABCD L

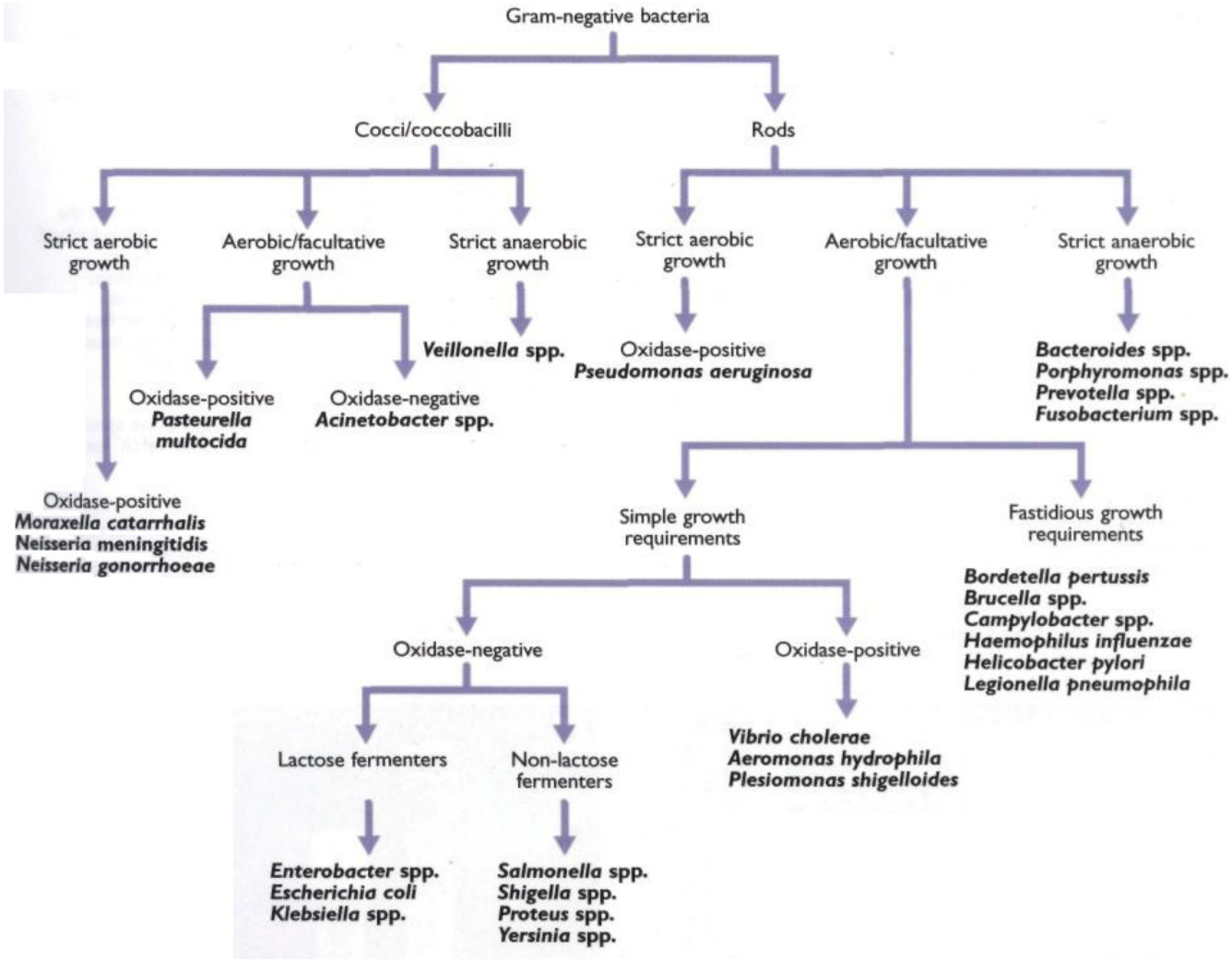
- Actinomyces
- Bacillus antracis (anthrax)
- Clostridium
- Diphtheria: Corynebacterium diphtheriae
- Listeria monocytogenes

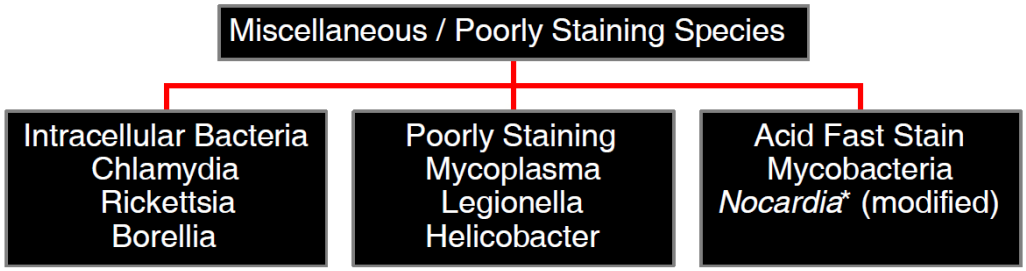
Remaining organisms are Gram negative rods


Gram Positive Bacteria
Cocci
Rods
Aerobic
Anaerobic
Aerobic
Anaerobic
Staphylococci
Streptococci
Enterococci
Peptostreptococci*
Bacillus*
Listeria
Nocardia*
Actinomyces
Clostridium


Gram-positive bacteria
Cocci
Rods
Aerobic/facultative growth
Strict anaerobic growth
Strict anaerobic growth
Aerobic/facultative growth
Catalase-positive
Catalase-negative
Branching
Spores
Catalase-positive
Catalase-negative
Clusters
Pairs/chains
Actinomyces spp.
Clostridium perfringens
Clostridium tetani
Clostridium botulinum
Lactobacillus spp.
Erysipelothrix spp.
Peptococcus spp.
Peptostreptococcus spp.
Coagulase-positive
Staphylococcus aureus
Coagulase-negative
Coagulase-negative staphylococci
Spores
Corynebacterium diphtheriae
Listeria monocytogenes
Enterococci (group D)
Enterococcus faecalis
Enterococcus faecium
Streptococci
Bacillus anthracis
Bacillus cereus
Bacillus subtilis
Alpha-haemolytic
Beta-haemolytic
Streptococcus pyogenes (groupA)
Streptococcus agalactiae (group B)
Streptococcus suis (group C)
Streptococcus bovis (group D)
Optochin
Resistant
Viridans type streptococci
Streptococcus anginosus
Streptococcus constellatus
Streptococcus intermedius
Streptococcus salivarius
Streptococcus sanguis
Sensitive
Streptococcus pneumoniae


Gram Negative Bacteria
Cocci
Rods
Aerobic Facultative Anaerobe
Anaerobic
Aerobic Facultative Anaerobe
Anaerobic
Neisseria
Branhamella*
Veillonella*
Enterobacteriaceae
Pseudomonas
Vibrio
Hemophilus
Bacteroides
Fusobacterium
Lactose fermenters
E. coli
Klebsiella
Nonlactose fermenters
Salmonella
Shigella


Gram-negative bacteria
Cocci/coccobacilli
Rods
Strict aerobic growth
Aerobic/facultative growth
Strict anaerobic growth
Strict aerobic growth
Aerobic/facultative growth
Strict anaerobic growth
Veillonella spp.
Oxidase-positive
Pseudomonas aeruginosa
Bacteroides spp.
Porphyromonas spp.
Prevotella spp.
Fusobacterium spp.
Oxidase-positive
Pasteurella multocida
Oxidase-negative
Acinetobacter spp.
Oxidase-positive
Moraxella catarrhalis
Neisseria meningitidis
Neisseria gonorrhoeae
Simple growth requirements
Fastidious growth requirements
Bordetella pertussis
Brucella spp.
Campylobacter spp.
Haemophilus influenzae
Helicobacter pylori
Legionella pneumophila
Oxidase-negative
Oxidase-positive
Lactose fermenters
Non-lactose fermenters
Vibrio cholerae
Aeromonas hydrophila
Plesiomonas shigelloides
Enterobacter spp.
Escherichia coli
Klebsiella spp.
Salmonella spp.
Shigella spp.
Proteus spp.
Yersinia spp.


Miscellaneous / Poorly Staining Species
Intracellular Bacteria
Chlamydia
Rickettsia
Borellia
Poorly Staining
Mycoplasma
Legionella
Helicobacter
Acid Fast Stain
Mycobacteria
Nocardia* (modified)

Antibiotics and aerobics/anerobics

Antibiotics with **anti-anaerobic** activity

- Penicillins
- Cephalosporins (except ceftazidime)
- Erythromycin
- Metronidazole
- Tetracycline

Antibiotics with **NO anti-anaerobic** activity

- Gentamicin
- Ciprofloxacin
- Ceftazidime

Incubation Periods: Questions may either ask directly about incubation periods or they may be used to provide a clue in a differential diagnosis

Less than 1 week

- Scarlet fever
- Influenza
- Diphtheria
- Meningococcus

1 - 2 weeks

- Malaria
- Measles
- Dengue fever
- Typhoid

2 - 3 weeks

- Mumps
- Rubella
- Chickenpox

Longer than 3 weeks

- Infectious mononucleosis
- Cytomegalovirus
- Viral hepatitis
- HIV

Vaccination: It is important to be aware of vaccines which are of the live-attenuated type as these may pose a risk to immunocompromised patient

Live attenuated vaccines

- BCG
- measles, mumps, rubella (MMR)
- oral polio
- oral typhoid*
- yellow fever

Whole killed organism/inactivated (injectable killed typhoid is no longer used in the UK)

- rabies
- influenza

Detoxified exotoxins

- tetanus

Fragment/Extracts of the organism or virus (may also be produced using recombinant DNA technology)

- diphtheria
- pertussis ('acellular' vaccine)
- heptitis B
- meningococcus, pneumococcus, hemophilus

Others

- influenza: different types are available, including whole inactivated virus, split virion (virus particles disrupted by detergent treatment) and sub-unit (mainly hemagglutinin and neuraminidase)
- cholera: contains inactivated Inaba and Ogawa strains of Vibrio cholerae together with recombinant B-subunit of the cholera toxin
- hepatitis B: contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology

Post-Exposure Prophylaxis

Hepatitis A

- Human Normal Immunoglobulin (HNIG) or hepatitis A vaccine may be used depending on the clinical situation

Hepatitis B

- HBsAg positive source: if the person exposed is a known responder to HBV vaccine then a booster dose should be given. If they are in the process of being vaccinated or are a non-responder they need to have hepatitis B immune globulin (HBIG) and the vaccine
- Unknown source: for known responders the green book advises considering a booster dose of HBV vaccine. For known non-responders HBIG + vaccine should be given whilst those in the process of being vaccinated you have an accelerated course of HBV vaccine

Hepatitis C

- Monthly PCR - if seroconversion then interferon +/- ribavirin

HIV

- A combination of oral antiretrovirals (e.g. Tenofovir, emtricitabine, lopinavir and ritonavir) as soon as possible (i.e. Within 1-2 hours, but may be started up to 72 hours following exposure) for 4 weeks
- Serological testing at 12 weeks following completion of post-exposure prophylaxis
- ↓ risk of transmission by 80%

Varicella zoster

- VZIG for IgG negative pregnant women/immunosuppressed

Tetanus vaccine is a cell-free purified toxin that is given as part of a combined vaccine (e.g. combined with diphtheria and inactivated polio vaccine)

Tetanus vaccine is currently given in the UK as part of the routine immunisation schedule at:

- 2 months
- 3 months
- 4 months
- 3-5 years
- 13-18 years

This therefore provides 5 doses of tetanus-containing vaccine. Five doses regimen is now considered to provide adequate long-term protection against tetanus.

Intramuscular human tetanus immunoglobulin should be given to patients with high-risk wounds (e.g. compound fractures, delayed surgical intervention, significant degree of devitalised tissue) irrespective of whether 5 doses of tetanus vaccine have previously been given

If vaccination history is incomplete or unknown then a dose of tetanus vaccine should be given combined with intramuscular human tetanus immunoglobulin for high-risk wounds

Tetanus is caused by the tetanospasmin exotoxin released from *Clostridium tetani*. Tetanus spores are present in soil and may be introduced into the body from a wound, which is often unnoticed. Tetanospasmin prevents release of GABA

Features

- Prodrome fever, lethargy, headache
- Trismus (lockjaw)
- Risus sardonicus
- Opisthotonus (arched back, hyperextended neck)
- Spasms (e.g. Dysphagia)

Management

- Supportive therapy including ventilatory support and muscle relaxants
- Intramuscular human tetanus immunoglobulin for high-risk wounds (e.g. Compound fractures, delayed surgical intervention, significant degree of devitalised tissue)
- Metronidazole is now preferred to benzylpenicillin as the antibiotic of choice

HIV

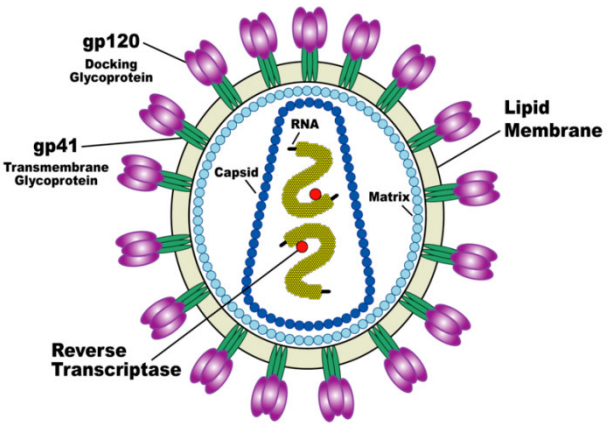
HIV seroconversion is symptomatic in 60-80% of patients and typically presents as a glandular fever type illness. ↑ symptomatic severity is associated with poorer long term prognosis. It typically occurs 3-12 weeks after infection

Man returns from trip abroad with maculopapular rash and flu-like illness - think HIV seroconversion

For questions involving businessmen always consider sexually transmitted infections

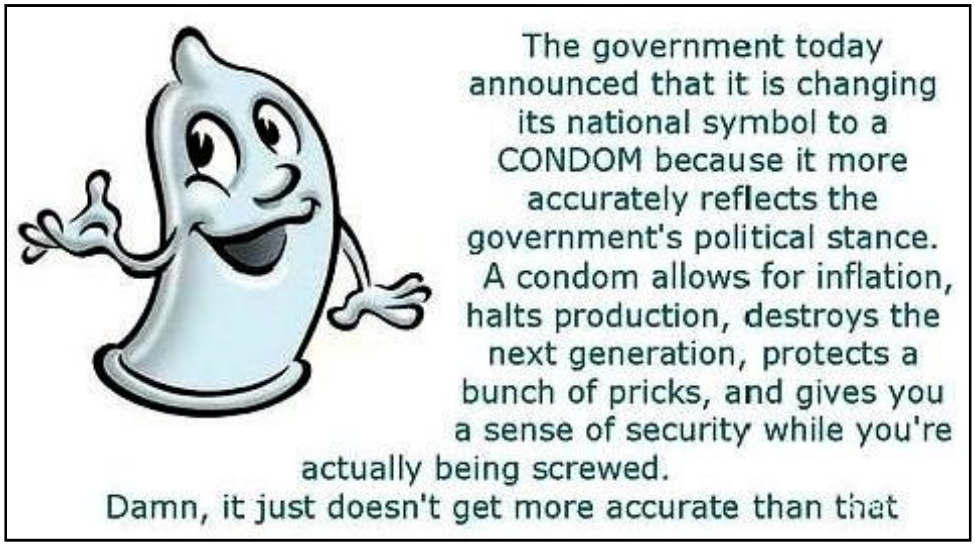
Features

- Sore throat
- Lymphadenopathy
- Malaise, myalgia, arthralgia
- Diarrhoea
- Maculopapular rash
- Mouth ulcers
- Rarely meningoencephalitis



Diagnosis

- Antibodies to HIV may not be present
- HIV PCR and p24 antigen tests can confirm diagnosis



HIV immunology:

The following immunological changes are seen in progressive HIV:

- Reduction in CD4 count
- **I**ncrease **B**2-**M**icroglobulin (IBM)
- **D**ecrease **IL**-2 production (DIL=DELL)
- Polyclonal B-cell activation
- ↓ NK cell function
- ↓ delayed hypersensitivity responses

} **IBM & DELL**

The Department of Health 'Greenbook' on immunisation defers to the British HIV Association for guidelines relating to immunisation of HIV-infected adults

Vaccines that can be used in all HIV-infected adults	Vaccines that can be used if CD4 > 200	Contraindicated in HIV-infected adults
Hepatitis A ▲ Hepatitis B ■ *Hemophilua* ■ *influenzae* B,HiB Influenza-parenteral ▲ Japanese encephalitis ▲ Meningococcus■-MenC Meningococcus■-ACWY I Pneumococcus■-PPV23 Poliomyelitis-parenteral (IPV) ▲ Rabies ▲ Tetanus-Diphtheria (TD)	Measles, Mumps, Rubella (MMR) ● Varicella● Yellow Fever●	Cholera* CVD103-HgR● Influenza-intranasal● Poliomyelitis-oral (OPV) ● Tuberculosis (BCG) ●

▲Whole killed organism/inactivated - ■Fragment/Extracts of the organism or virus - ●Live attenuated vaccines
*Most of other types of cholera vaccine are killed

Diarrhea is common in patients with HIV. This may be due to the effects of the virus itself (HIV enteritis) or opportunistic infections

Possible causes

- Cryptosporidium + other protozoa (most common)
- Cytomegalovirus
- *Mycobacterium avium intracellulare*
- Giardia

Cryptosporidium is the most common infective cause of diarrhoea in HIV patients. It is an intracellular protozoon and has an incubation period of 7 days. Presentation is very variable, ranging from mild to severe diarrhoea. A modified Ziehl-Neelsen stain (**acid-fast stain**) of the stool may reveal the characteristic red cysts of Cryptosporidium. Molecular methods are currently used mainly as a research tool. Treatment is difficult, with the mainstay of management being supportive therapy. (nitazoxanide is licensed in the US for immunocompetent patients)

Mycobacterium avium intracellulare is an atypical mycobacteria seen with the CD4 count is below 50. Typical features include fever, sweats, abdominal pain and diarrhoea. There may be hepatomegaly and deranged LFTs. Diagnosis is made by blood cultures and bone marrow examination. Management is with rifampicin, ethambutol and clarithromycin

Pregnancy: with the ↑ incidence of HIV infection amongst the heterosexual population there are an increasing number of HIV positive women giving birth in the UK. In London the incidence may be as

high as 0.4% of pregnant women. The aim of treating HIV positive women during pregnancy is to minimise harm to both the mother and fetus, and to ↓ the chance of vertical transmission.

Factors which ↓ vertical transmission (from 25-30% to 2%)

- Maternal antiretroviral therapy
- Mode of delivery (caesarean section)
- Neonatal antiretroviral therapy
- Infant feeding (bottle feeding)

Screening

- NICE guidelines recommend offering HIV screening to all pregnant women

Antiretroviral therapy

- All pregnant women should be offered antiretroviral therapy regardless of whether they were taking it previously
- If women are not currently taking antiretroviral therapy it is **usually commenced between 28 and 32 weeks of gestation** and should be continued intrapartum

Mode of delivery

- Elective caesarean section*
- A zidovudine infusion should be started four hours before beginning the caesarean section

Neonatal antiretroviral therapy

- Zidovudine is usually administered orally to the neonate for four to six weeks

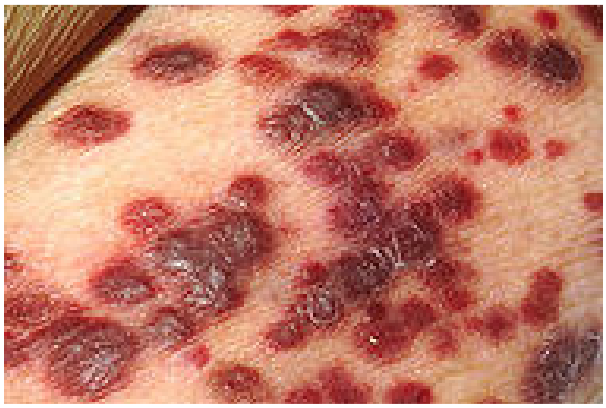
Infant feeding

- In the UK all women should be advised not to breast feed

*the 2008 BHIVA guidelines suggest vaginal delivery may be an option for women on HAART who have an undetectable viral load but whether this will translate into clinical practice remains to be seen

Kaposi's sarcoma

- Caused by HHV-8 (Human Herpes Virus 8)
- Presents as purple papules or plaques on the skin or mucosa (e.g. Gastrointestinal and respiratory tract)
- Skin lesions may later ulcerate
- Respiratory involvement may cause massive hemoptysis and pleural effusion
- Radiotherapy + resection



***Pneumocystis carinii* pneumonia:** whilst the organism *Pneumocystis carinii* is now referred to as Pneumocystis jiroveci, the term *Pneumocystis carinii* pneumonia (PCP) is still in common use

- Pneumocystis jiroveci is an unicellular eukaryote, generally classified as a fungus but some authorities consider it a protozoa
- PCP is the most common opportunistic infection in AIDS
- All patients with a CD4 count < 200/mm³ should receive PCP prophylaxis

Features

- Dyspnea
- Dry cough
- Fever
- Very few chest signs

Extrapulmonary manifestations are rare (1-2% of cases), may cause

- Hepatosplenomegaly
- Lymphadenopathy
- Choroid lesions

Immune Reconstitution Uveitis: occurs in AIDS in response to immune system recovery, there is granulamtous uveitis that leads to reduced vision and eye discoloration

Investigation

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal
- Exercise-induced desaturation
- Sputum often fails to show PCP, bronchoalveolar lavage (BAL) often needed to demonstrate PCP (silver stain)

Management

- Co-trimoxazole
- IV pentamidine in severe cases
- Steroids if hypoxic (if $pO_2 < 9.3$kpa then steroids ↓ risk of respiratory failure by 50% and death by a third)

The most common cause of biliary disease in patients with HIV is sclerosing cholangitis due to infections such as CMV, Cryptosporidium and Microsporidia
Pancreatitis in the context of HIV infection may be secondary to anti-retroviral treatment (especially didanosine) or by opportunistic infections e.g. CMV

Meningitis

The table below summarises the characteristic cerebrospinal fluid (CSF) findings in meningitis:

	Bacterial	**Viral**	**Tuberculous**
Appearance	Cloudy	Clear/cloudy	Fibrin web
Glucose	Low (< 1/2 plasma)	Normal*	Low (< 1/2 plasma)
Protein	High (> 1 g/l)	Normal/raised	High (> 1 g/l)
White cells/mm³	10 - 5,000 polymorphs	15 - 1,000 lymphocytes	10 - 1,000 lymphocytes

The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore PCR is sometimes used (sensitivity = 75%)

*mumps is unusual in being associated with a low glucose level in a proportion of cases. A low glucose may also be seen in herpes encephalitis

Management

Meningococcus

- If penicillin allergic then give chloramphenicol
- If there is **NO A HISTORY OF ANAPHYLAXIS** then **cefotaxime** may be considered for penicillin allergic patients

Management of contacts

- Prophylaxis needs to be offered to household and close contacts of patients affected with meningococcal meningitis
- Rifampicin or ciprofloxacin may be used
- The risk is highest in the first 7 days but persists for at least 4 weeks
- Meningococcal vaccination should be offered when serotype results are available, for close contacts who have not previously been vaccinated*

*no vaccine is available for meningococcal serogroup B

Meningococcal septicemia:

Investigations

- Blood cultures
- Blood PCR, if antibiotic was already started.
- Lumbar puncture is usually contraindicated
- Full blood count and clotting to assess for disseminated intravascular coagulation

Streptococci may be divided into α and β hemolytic types

α hemolytic streptococci
The most important α hemolytic *Streptococcus* is *Streptococcus pneumoniae* (pneumococcus). Pneumococcus is a common cause of pneumonia, meningitis and otitis media. Another clinical example is *Streptococcus viridans*
β hemolytic streptococci
Group A
• Most important organism is *Streptococcus pyogenes* • Responsible for erysipelas, impetigo, cellulitis, type 2 necrotizing fasciitis & pharyngitis/tonsillitis • Immunological reactions can cause rheumatic fever or post-streptococcal glomerulonephritis • Erythrogenic toxins cause scarlet fever • **Penicillin is the antibiotic of choice for group A streptococcal infections**
Group B
• *Streptococcus agalactiae* may lead to neonatal meningitis and septicemia

Cellulitis: the BNF recommends penicillin + flucloxacillin as first-line treatment for cellulitis. Erythromycin is recommended in patients allergic to penicillin. Treatment failure is now commonly treated with oral clindamycin.

Staphylococcal toxic shock syndrome describes a severe systemic reaction to staphylococcal exotoxins. It came to prominence in the early 1980's following a series of cases related to infected tampons

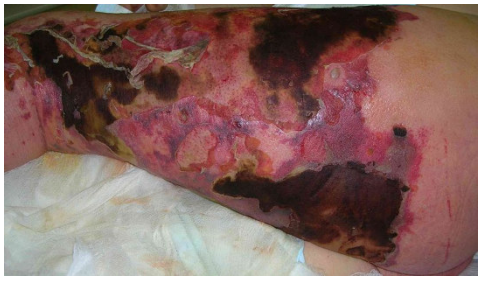
Centers for Disease Control and Prevention diagnostic criteria

- Fever: temperature > 38.9ºc
- Hypotension: systolic blood pressure < 90 mmHg
- Diffuse erythematous rash
- Desquamation of rash, especially of the palms and soles
- Involvement of three or more organ systems: e.g. Gastrointestinal (diarrhoea and vomiting), mucous membrane erythema, renal failure, hepatitis, thrombocytopenia, CNS involvement (e.g. Confusion)

Necrotising fasciitis is a medical emergency that is difficult to recognise in the early stages

It can be classified according to the **causative organism**:

- Type 1 is caused by mixed anaerobes and aerobes (often occurs post-surgery in diabetics)
- Type 2 is caused by *Streptococcus pyogenes*



Features

- Acute onset
- Painful, erythematous lesion develops (cellulitis like)
- Extremely tender over infected tissue

Management

- Urgent surgical debridement
- IV antibiotics

Listeria monocytogenes is a Gram positive bacillus which has the unusual ability to multiply at low temperatures. It is typically spread via contaminated food, typically unpasteurised dairy products. Infection is particularly dangerous to the unborn child where it can lead to miscarriage

Features - can present in a variety of ways

- Diarrhoea, flu-like illness
- Pneumonia , meningoencephalitis
- Ataxia and seizures

Suspected Listeria infection should be investigated by taking blood cultures. CSF may reveal a **pleocytosis, with 'tumbling motility' on wet mounts**

Management

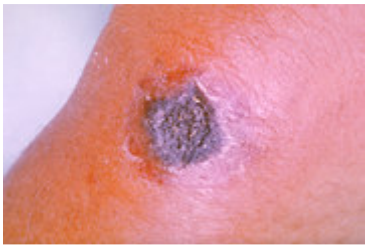
- Listeria is sensitive to amoxicillin/ampicillin (cephalosporins usually inadequate)
- Listeria meningitis should be treated with IV amoxicillin/ampicillin and gentamicin

---

Anthrax is caused by Bacillus anthracis, a Gram positive rod. It is spread by infected carcasses

Features

- Causes painless black eschar (cutaneous 'malignant pustule', but no pus)
- Typically painless and non-tender
- May cause marked edema
- Anthrax can cause gastrointestinal bleeding



Management

- The current Health Protection Agency advice for the initial management of cutaneous anthrax is ciprofloxacin
- Further treatment is based on microbiological investigations and expert advice

---

MRSA: Methicillin-resistant *Staphylococcus aureus* (MRSA) was one of the first organisms which highlighted the dangers of hospital-acquired infections.

Who should be screened for MRSA?

- All patients awaiting elective admissions (exceptions include day patients having terminations of pregnancy and ophthalmic surgery. Patients admitted to mental health trusts are also excluded)
- From 2011 all emergency admissions will be screened

How should a patient be screened for MRSA?

- Nasal swab and skin lesions or wounds
- The swab should be wiped around the inside rim of a patient's nose for 5 seconds
- The microbiology form must be labelled 'MRSA screen'

Suppression of MRSA from a carrier once identified

- Nose: mupirocin 2% in white soft paraffin, TDS for 5 days
- Skin: chlorhexidine gluconate, OD for 5 days. Apply all over but particularly to the axilla, groin and perineum

The following antibiotics are commonly used in the treatment of MRSA infections:

- Vancomycin
- Teicoplanin

Some strains may be sensitive to the antibiotics listed below but they should not generally be used alone because resistance may develop:

- Rifampicin
- Macrolides
- Tetracyclines
- Aminoglycosides
- Clindamycin

Relatively new antibiotics such as linezolid, quinupristin/dalfopristin combinations and tigecycline have activity against MRSA but should be reserved for resistant cases

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Legionnaire's disease is caused by the intracellular bacterium *Legionella pneumophilia*. It is typically colonizes water tanks and hence questions may hint at air-conditioning systems or foreign holidays. Person-to-person transmission is not seen

Features	Diagnosis	Management
• Flu-like symptoms • Dry cough • Lymphopenia • Hyponatremia • Deranged LFTs	• Urinary antigen	• Treat with erythromycin

---

Leptospirosis (Weil's disease) leptospirosis is commonly seen in questions referring to sewage workers, farmers, vets or people who work in abattoir. It is caused by the spirochaete Leptospira interrogans (serogroup L icterohemorrhagiae), classically being spread by contact with infected rat urine. Weil's disease should always be considered in high-risk patients with hepatorenal failure. The term Weil's disease referrs for the most severe 10% of cases of leptospirosis associated with jaundice

Features

- Fever
- Flu-like symptoms → **WITHOU PRODUCTIVE COUGH**
- Renal failure (seen in 50% of patients)
- Jaundice
- Subconjunctival hemorrhage
- Headache, may herald the onset of meningitis

Management

- A lumbar puncture should ideally be done first to confirm meningeal involvement, if there are meningeal symptoms.
- High-dose benzylpenicillin or doxycycline

Acute epiglottitis is rare but serious infection caused by *Hemophilus influenzae* type B. Prompt recognition and treatment is essential as airway obstruction may develop. Epiglottitis generally occurs in children between the ages of 2 and 6 years. The incidence of epiglottitis has ↓ since the introduction of the Hib vaccine

Features

- Rapid onset
- Unwell, toxic child
- Stridor
- Drooling of saliva

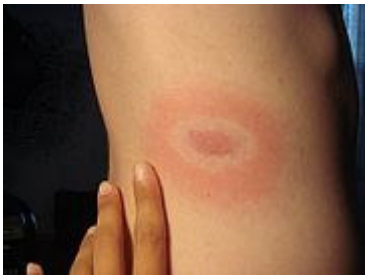
Lyme Disease: or borreliosis is an emerging infectious disease caused by at least three species of bacteria belonging to the genus Borrelia. Borrelia burgdorferi sensu stricto is the main cause of Lyme disease in the United States, whereas Borrelia afzelii and Borrelia garinii cause most European cases.

Early features

- Erythema chronicum migrans (small papule often at site of the tick bite which develops into a larger annular lesion with central clearing, occurs in 70% of patients)
- Systemic symptoms: malaise, fever, arthralgia

Later features

- CVS: heart block, myocarditis
- Neurological: cranial nerve palsies, meningitis
- Polyarthritis



Characteristic "bulls-eye" rash caused by Lyme disease

TB & Anti-TB therapy:

Overview

- Heaf test is done in UK to see if BCG is needed, used for screening
- Mantoux test is considered more accurate

Mantoux test

- Immune mediated type IV hypersensitivity reaction
- Ml of 1:1,000 purified protein derivative (PPD) injected intradermally
- Result read 2-3 days later
- Erythema & induration > 10mm = positive result - this implies previous exposure including BCG

Heaf test classically involves injection of PPD equivalent to 100,000 units per ml to the skin over the flexor surface of the left forearm. It is then read 3-10 days later

Negative	No induration, maybe 6 minute puncture scars
Grade 1	4-6 puncture sites are indurated
Grade 2	Confluent puncture sites form indurated ring
Grade 3	Extensive induration to form disc (5-10 mm)
Grade 4	Severe induration > 10 mm with or without blistering

Grades 1 and 2 may be the result of previous BCG or avian tuberculosis whilst grades 3 or 4 require a CXR and follow-up

False negative tests may be caused by:

- Miliary TB
- Sarcoidosis
- HIV
- Lymphoma
- Very young age (e.g. < 6 months)

Treatment:

The standard therapy for treating **active tuberculosis** is:
Initial phase - first 2 months (RIPE)
• Rifampicin • Isoniazid • Pyrazinamide • Ethambutol (in 2006 NICE recommend giving a 'fourth drug' such as ethambutol routinely - previously this was only added if drug-resistant tuberculosis was suspected)
Continuation phase - next 4 months
• Rifampicin • Isoniazid
Latent tuberculosis:
isoniazid alone for 6 months
Meningeal tuberculosis:
prolonged period (at least 12 months) with the addition of steroids
Directly observed therapy 3 per week dosing regimen may be indicated in certain groups, including:
• Homeless people with active tuberculosis • Patients who are likely to have poor concordance • All prisoners with active or latent tuberculosis

Streptomycin: (aminogycoside) used in resistant TB

Anti-TB Common side effects:

Rifampicin	
• Potent liver enzyme inducer • Hepatitis	• Orange secretions • Flu-like symptoms
Isoniazid	
• Peripheral neuropathy: prevent with pyridoxine (Vitamin B6) • May also cause optic neuritis but it is not as common a cause as ethambutol. • Hepatitis, agranulocytosis • Liver enzyme inhibitor	
Pyrazinamide	
• Hyperuricemia causing gout	• Hepatitis
Ethambutol	
• Optic neuritis: check visual acuity before and during treatment • Dose needs adjusting in patients with renal impairment	
Streptomycin	
• **V**estibular damage → **V**ertigo and **V**omiting • Cochlear damage → deafness	• Angioedema or angioneuritic edema • Nephrotoxicosis

Asymptomatic patient with Hx of TB exposure and Heaf Test positive are recommended for dual therapy for 5 months or INH for 6 months.

Leprosy: Hansen's disease (HD) is a chronic disease caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*.

Features:

- Nodular skin lesions
- Erythremaous raised plaque like lesions in arms and legs

Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs, and eyes.

Management:

- Skin biopsy and needle test in cold area (ear lobuleand elbow)
- Pauci-bacillary leprosy (<5 lesions) Treat with rifampicin and dapsone for 6 months
- Multi-bacillary leprosy (>5 lesions) → rifampicin, clofazimine and dapsone for 12 months

Malaria:

Feature of severe malaria	**Complications**
• Schizonts on a blood film • Parasitemia > 2% • Hypoglycemia • Temperature > 39 °c • Severe anemia • Complications as below	• Cerebral malaria: seizures, coma • ARF: blackwater fever, secondary to intravascular hemolysis, mechanism unknown • Acute respiratory distress syndrome (ARDS) • Hypoglycemia • Disseminated intravascular coagulation (DIC)

Uncomplicated falciparum malaria

- Strains resistant to chloroquine are prevalent in certain areas of Asia and Africa
- WHO 2010 guidelines: artemisinin-based combination therapies (ACTs) as first-line therapy
- Examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine

Severe falciparum malaria

- A parasite counts >2% will usually need parenteral treatment irrespective of clinical state
- IV artesunate is now recommended by WHO in preference to intravenous quinine (2010 guidelines)
- If parasite count > 10% then exchange transfusion should be considered
- Shock may indicate coexistent bacterial septicemia - malaria rarely causes hemodynamic collapse

↑ Respiratory rate indicate acute respiratory distress syndrome (ARDS), a feared complication of falciparum malaria.

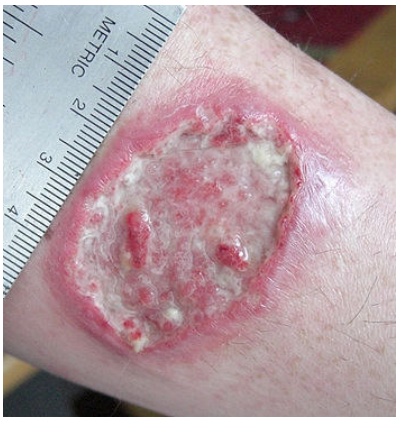
Non-falciparum malaria the most common cause is *Plasmodium vivax*, with *Plasmodium ovale* and *Plasmodium malariae* accounting for the other cases. *Plasmodium vivax* is often found in Central America and the Indian Subcontinent whilst *Plasmodium ovale* typically comes from Africa

Benign malarias have a hypnozoite stage and may therefore relapse following treatment

Treatment

- Non-falciparum malarias are almost always chloroquine sensitive
- Primaquine should be used in *Plasmodium vivax* and *Plasmodium ovale* infection to destroy liver hypnozoites

Leishmaniasis is caused by the intracellular protozoa Leishmania, usually being spread by sand flies. The organism multiply in monocytes and macrophages, its incubation period may extend upto 10 years. 3 forms are seen as following:



Cutaneous leishmaniasis

- Caused by *Leishmania tropica* or *Leishmania mexicana*
- Crusted lesion at site of bite
- May be underlying ulcer

Mucocutaneous leishmaniasis

- Caused by Leishmania brasiliensis
- Skin lesions may spread to involve mucosae of nose, pharynx…

Visceral leishmaniasis (kala-azar)

- Mostly caused by Leishmania donovani
- Occurs in Mediterranean, Asia, South America, Africa
- Fever (typically ↑ twice in 24hours), sweats, rigors
- Massive splenomegaly, hepatomegaly
- Pancytopenia secondary to hypersplenism
- Poor appetite*, weight loss
- Grey skin - 'kala-azar' means black sickness or black fever

*occasionally patients may report ↑ appetite with paradoxical weight loss

---

Trypanosomiasis: Two main form of this protozoal disease are recognised - African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas' disease)

Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen - Trypanosoma gambiense in West Africa and *Trypanosoma rhodesiense* in East Africa. Both types are spread by the tsetse fly.

Trypanosoma rhodesiense tends to follow a more acute course. **Clinical features** include:

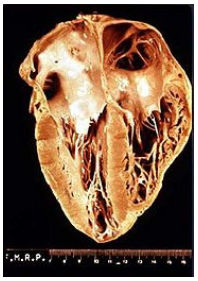
- Trypanosoma chancre - tender subcutaneous nodule at site of infection
- Enlargement of posterior cervical lymph nodes
- Later: central nervous system involvement e.g. Meningoencephalitis

Management

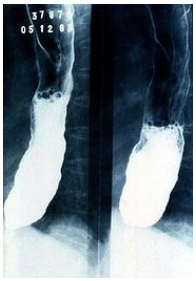
- Early disease: IV pentamidine or suramin
- Later disease or central nervous system involvement: IV melarsoprol

American trypanosomiasis, or **Chagas' disease**, is caused by the protozoan *Trypanosoma cruzi*. (95%) of patients are asymptomatic in the acute phase although a chagoma (an erythematous nodule at site of infection) and periorbital edema are sometimes seen. Chronic Chagas' disease mainly affects the heart and gastrointestinal tract

periorbital edema



Myocardium with chagas



Chagas megaesophagus

Complications:

- Myocarditis may lead to heart failure and arrhythmias. (leading cause of death)
- Gastrointestinal features includes megaesophagus and megacolon causing dysphagia and constipation

Management

- Treatment is most effective in the acute phase using azole or nitroderivatives such as benznidazole or nifurtimox
- Chronic disease management involves treating the complications e.g. heart failure

---

Schistosomiasis, or Bilharzia, is a parasitic flatworm infection. The following types of schistosomiasis are recognised:

- Schistosoma mansoni and Schistosoma intercalatum: intestinal schistosomiasis
- Schistosoma Hematobium: urinary schistosomiasis

Schistosoma **hem**atobium causes **hem**aturia

Schistosoma Hematobium

This typically presents as a 'swimmer's itch' in patients who have recently returned from Africa. Schistosoma Hematobium is a risk factor for squamous cell bladder cancer

Schistosomiasis is a risk factor for **S**quamous cell bladder cancer

Features

- Frequency
- Hematuria
- Bladder calcification

Management
Single oral dose of praziquantel

Rabies:

- Prodrome: headache, fever, agitation
- Hydrophobia: water-provoking muscle spasms
- Hypersalivation

There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries. Following an animal bite in at risk countries:

- If an individual is already immunised then 2 further doses of vaccine should be given
- If not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination

---

Animal Bites:

Management

- Cleanse wound
- Current BNF recommendation is co-amoxiclav
- If penicillin-allergic then doxycycline + metronidazole is recommended

---

Cat scratch disease is generally caused by the Gram negative rod *Bartonella henselae*

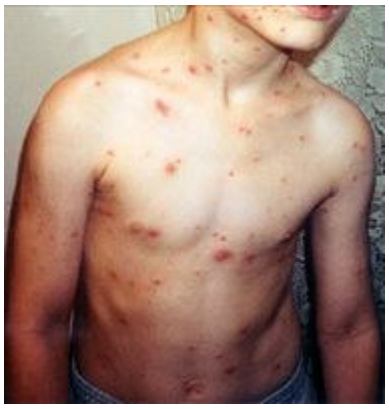
Features

- fever
- history of a cat scratch
- regional lymphadenopathy
- headache, malaise

Chickenpox is caused by primary infection with varicella zoster virus. Shingles is reactivation of dormant virus in dorsal root ganglion. Varicella zoster virus is the **MOST CONTAGIOUS ORGANISM**.

Chickenpox is highly infectious

- Spread via the respiratory route
- Can be caught from someone with shingles
- Infectivity = 4 days before rash, until 5 days after the rash first appeared (traditionally taught patients were infective until all lesions had scabbed over)
- Incubation period = 11-21 days

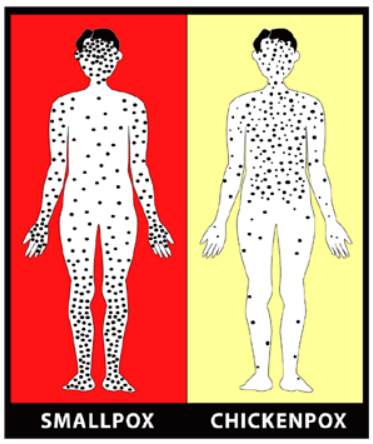


Clinical features (tend to be more severe in older children/adults)

- Fever initially
- Itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular
- Systemic upset is usually mild

Management is supportive

- Keep cool, trim nails
- Calamine lotion
- School exclusion: current HPA advice is 5 days from start of skin eruption. They also state 'Traditionally children have been excluded until all lesions are crusted. However, transmission has never been reported beyond the fifth day of the rash.'
- Immunocompromised patients and newborns with peripartum exposure should receive varicella zoster immunoglobulin (VZIG). **If chickenpox develops then IV aciclovir should be considered**



A **common complication** is secondary bacterial infection of the lesions. Rare complications include:

- Pneumonia: varicella pneumonia is the most common and serious complication of chickenpox infection in adults. Auscultation of the chest is often unremarkable → IV acyclovir
- Encephalitis (cerebellar involvement may be seen)
- Disseminated hemorrhagic chickenpox
- Arthritis, nephritis and pancreatitis may very rarely be seen

In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome

Chickenpox exposure in pregnancy - first step is to check antibodies

Fetal varicella syndrome (FVS)

- Risk of FVS following maternal varicella exposure is around 1% if occurs before 20 weeks gestation
- Studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks
- Features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities

Management of chickenpox exposure

- If there is any doubt about the mother previously having chickenpox maternal blood should be checked for varicella antibodies
- If the pregnant woman is not immune to varicella she should be given varicella zoster immunoglobulin (VZIG) as soon as possible. RCOG and Greenbook guidelines suggest VZIG is effective up to 10 days post exposure
- Consensus guidelines suggest oral aciclovir should be given if pregnant women with chickenpox present within 24 hours of onset of the rash

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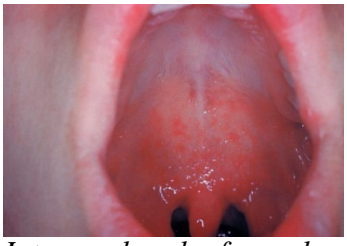
Measles

Overview

- **RNA paramyxovirus**
- Spread by droplets
- Infective from prodrome until 5 days after rash starts
- Incubation period = 10-14 days



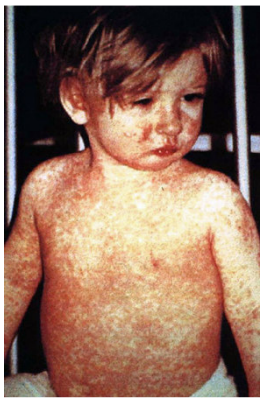
Intra oral rash of measles

Features

- Prodrome: irritable, conjunctivitis, fever
- Koplik spots (before rash): white spots ('grain of salt') on buccal mucosa
- Rash: starts behind ears then to whole body, discrete maculopapular rash becoming blotchy & confluent

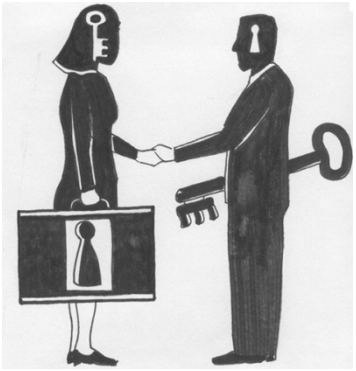
Complications

- Encephalitis: typically occurs 1-2 weeks after the onset of the illness.
- Subacute sclerosing panencephalitis: very rare, may present 5-10 years following the illness
- Febrile convulsions
- Pneumonia, tracheitis
- Keratoconjunctivitis, corneal ulceration
- Diarrhoea
- ↑ incidence of appendicitis
- Myocarditis



Management of contacts

- If a child not immunized against measles comes into contact with measles then MMR should be offered (vaccine-induced measles antibody develops more rapidly than that following natural infection)
- This should be given within 72 hours

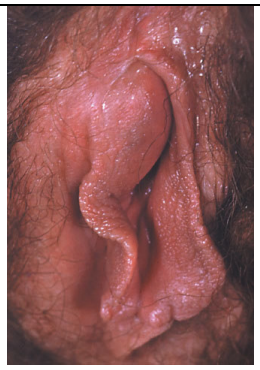


Gonorrhoea is caused by the Gram negative diplococcus *Neisseria* gonorrhoea. Acute infection can occur on any mucous membrane surface, typically genitourinary but also rectum and pharynx. The incubation period of gonorrhoea is 2-5 days

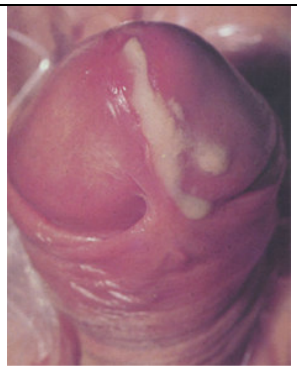
Features

- ♂s: urethral discharge, dysuria
- ♀s: cervicitis e.g. Leading to vaginal discharge
- Rectal and pharyngeal infection is usually asymptomatic, but may present as rectal bleeding

Local complications that may develop include urethral strictures, epididymitis and salpingitis (hence may lead to infertility). Disseminated infection may occur - see below



Gonococcal urethritis is among the most common causes of Bartholin gland abcesses, which cause pain and labial swelling



Symptomatic gonococcal urethritis typically presents with penile discharge and dysuria within 2 weeks of exposure

Management

- Ciprofloxacin 500mg PO used to be the treatment of choice
- However, there is ↑ resistance to ciprofloxacin and therefore **cephalosporins** are now used
- Options include cefixime 400mg PO (single dose) or ceftriaxone 250mg IM

Disseminated gonococcal infection (DGI) and gonococcal arthritis may also occur, with gonococcal infection being the most common cause of septic arthritis in young adults. The pathophysiology of DGI is not fully understood but is thought to be due to Hematogenous spread from mucosal infection (e.g. asymptomatic genital infection). Initially there may be a classic **triad of symptoms: tenosynovitis, migratory polyarthritis and dermatitis**. Later complications include septic arthritis, endocarditis and perihepatitis (Fitz-Hugh-Curtis syndrome)

Key features of disseminated gonococcal infection

- Tenosynovitis
- Migratory polyarthritis
- Dermatitis (lesions can be maculopapular or vesicular)

Genital warts (also known as condylomata accuminata) are a common cause of attendance at genitourinary clinics. They are caused by the many varieties of the human papilloma virus HPV, especially types 6 & 11. It is now well established that HPV (primarily types 16, 18 & 33) predisposes to cervical cancer.

Features

- Small (2 - 5 mm) fleshy protuberances which are slightly pigmented
- May bleed or itch

Management

- Topical podophyllum or cryotherapy are commonly used as first-line treatments depending on the location and type of lesion. Multiple, non-keratinised warts are generally best treated with topical agents whereas solitary, keratinised warts respond better to cryotherapy
- Imiquimod is a topical cream which is generally used second line
- Genital warts are often resistant to treatment and recurrence is common although the majority of anogenital infections with HPV clear without intervention within 1-2 years

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Genital Ulcers: genital herpes is most often caused by the herpes simplex virus (HSV) type 2 (cold sores are usually due to HSV type 1). Primary attacks are often severe and associated with fever whilst subsequent attacks are generally less severe and localised to one site

Genital ulcers

- Painful: herpes **>>** chancroid
- Painless: syphilis **>** lymphogranuloma venereum + granuloma inguinale

Syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*. Infection is characterized by primary, secondary and tertiary stages. A painless ulcer (chancre) is seen in the primary stage. The incubation period= 9-90 days

Primary features

- Chancre - painless ulcer at the site of sexual contact
- Often not seen in women

Secondary features - occurs 4-10 weeks after primary infection

- Systemic symptoms: fevers, lymphadenopathy
- Rash on trunk, palms and soles
- Buccal 'snail track' ulcers (30%)
- Condylomata lata

Latent period

Tertiary features

- Gummas
- Aortic aneurysms
- General paralysis of the insane
- Tabes dorsalis (slow degeneration of the sensory neurons. The degenerating nerves are in the dorsal column; proprioception, vibration, and fine touch).

Treponema pallidum is a very sensitive organism and cannot be grown on artificial media. The diagnosis is therefore usually based on clinical features; serology and microscopic examination of infected tissue

Serological tests can be divided into

- Cardiolipin tests (not treponeme specific)
- Treponemal specific antibody tests

Cardiolipin tests

- Syphilis infection leads to the production of non-specific antibodies that react to cardiolipin
- Examples include VDRL (venereal disease research laboratory) & RPR (rapid plasma reagin)
- Insensitive in late syphilis
- Becomes negative after treatment

Treponemal specific antibody tests

- Example: TPHA (*Treponema pallidum* hemagglutination test)
- Remains positive after treatment

Causes of false positive cardiolipin tests

- Pregnancy
- SLE, anti-phospholipid syndrome
- TB
- Leprosy
- Malaria
- HIV

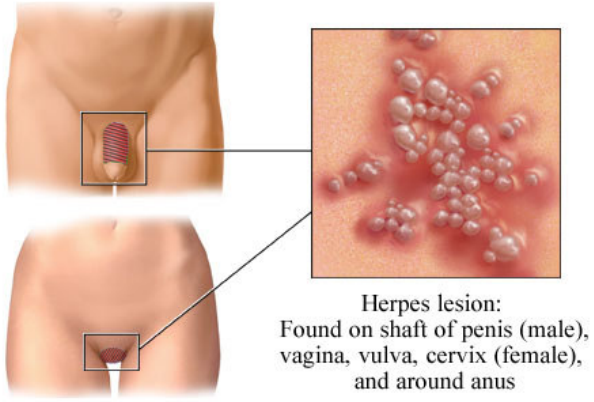
Lymphogranuloma venereum is caused by *Chlamydia trachomatis*. Typically infection comprises of three stages

- Stage 1: small painless pustule which later forms an ulcer
- Stage 2: painful inguinal lymphadenopathy
- Stage 3: proctocolitis

Herpes Simplex Virus: there are two strains of the (HSV) in humans: HSV-1 and HSV-2. Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap

Features

- Primary infection: may present with a severe gingivostomatitis
- Cold sores
- **Painful genital ulceration**



Herpes lesion:
Found on shaft of penis (male), vagina, vulva, cervix (female), and around anus

Management:

- Gingivostomatitis: oral aciclovir, chlorhexidine mouthwash
- Cold sores: topical aciclovir although the evidence base for this is modest
- Genital herpes: oral aciclovir. Some patients with frequent exacerbations may benefit from longer term aciclovir

Other causes of genital ulcers

- Behcet's disease
- Carcinoma
- Granuloma inguinale: *Klebsiella granulomatis* (previously called *Calymmatobacterium granulomatis*)

Chancroid is a tropical disease caused by *Hemophilus ducreyi*. It causes painful genital ulcers associated with inguinal lymph node enlargement.

Chancre	Chancroid
Treponema pallidum	Haemophilus ducreyi
Painless	Painful
Non-exudative	Grey or yellow purulent exudate
Hard (indurated) edge	Soft edge
Heal spontaneously within 3 - 6 weeks, even in the absence of treatment	
Can occur in the pharynx as well as on the genitals	

Vaginal discharge is a common presenting symptom and is not always pathological

Common causes

- Physiological
- *Candida*
- *Trichomonas vaginalis*
- Bacterial vaginosis

Less common causes

- Whilst cervical infections such as *Chlamydia* and Gonorrhoea can cause a vaginal discharge this is rarely the presenting symptoms
- Ectropion
- Foreign body
- Cervical cancer

Key features of the common causes are listed below

Condition	Key features
Candida	'Cottage cheese' discharge Vulvitis Itch
Trichomonas vaginalis	Offensive, yellow/green, frothy discharge Vulvovaginitis Strawberry cervix
Bacterial vaginosis	**Offensive, thin, white/grey, 'fishy' discharge**

Bacterial vaginosis (BV) describes an overgrowth of predominately **anaerobic organisms** such as Gardnerella vaginalis. This leads to a consequent fall in lactic acid producing aerobic lactobacilli resulting in a raised vaginal pH. Whilst it's not a sexually transmitted infection it is seen almost exclusively in sexually active women.

Amsel's criteria for diagnosis of BV - 3 of the following 4 points should be present:

- Thin, white homogenous discharge
- Clue cells on microscopy
- Vaginal pH > 4.5
- Positive whiff test (addition of potassium hydroxide results in fishy odour)

Features

- Vaginal discharge: 'fishy', offensive
- Asymptomatic in 50%

Bacterial vaginosis in pregnancy

- Results in an increased risk of preterm labour, low birth weight and chorioamnionitis, late miscarriage
- It was previously taught that oral metronidazole should be avoided in the 1st trimester and topical clindamycin used instead. Recent guidelines however recommend: oral metronidazole is used throughout pregnancy. BNF is against the use of high dose metronidazole regimes

Management

- Oral metronidazole for 5-7 days
- 70-80% initial cure rate
- Relapse rate > 50% within 3 months

Chlamydia is the most prevalent sexually transmitted infection in the UK and is caused by *Chlamydia trachomatis*, an obligate intracellular pathogen. Approximately 1 in 10 young women in the UK have *Chlamydia.* The incubation period is around 7-21 days, although it should be remembered a large percentage of cases are asymptomatic

Features

- Asymptomatic in around 70% of women and 50% of ♂s
- Women: cervicitis (discharge, bleeding), dysuria
- Men: urethral discharge, dysuria

Potential complications

- Epididymitis
- Pelvic inflammatory disease
- Endometritis
- ↑ incidence of ectopic pregnancies
- Infertility
- Reactive arthritis
- Perihepatitis (Fitz-Hugh-Curtis syndrome)

Investigation

- Traditional cell culture is no longer widely used
- Nuclear Acid Amplification Tests (NAATs) are now rapidly emerging as the investigation of choice
- Urine (first void urine sample), vulvovaginal swab or cervical swab may be tested using the NAAT technique

Gonorrhoea would be demonstrated by the presence of Gram negative diplococci on the swab. If the swab showed non-specific urethritis a diagnosis of *Chlamydia* is most likely. Both many times infect together

Screening

- In England the National *Chlamydia* Screening Programme is open to all men and women aged 15-24 years
- The 2009 SIGN guidelines support this approach, suggesting screening all sexually active patients aged 15-24 years
- Relies heavily on opportunistic testing

Management

- Doxycycline (7 day course) or azithromycin (single dose). The 2009 SIGN guidelines suggest azithromycin should be used first-line due to potentially poor compliance with a 7 day course of doxycycline
- If pregnant then erythromycin or amoxicillin may be used. The SIGN guidelines suggest considering azithromycin 'following discussion of the balance of benefits and risks with the patient'
- Patients diagnosed with *Chlamydia* should be offered a choice of provider for initial partner notification - either trained practice nurses with support from GUM, or referral to GUM
- For men with symptomatic infection all partners from 4 weeks prior to the onset of symptoms should be contacted
- For women and asymptomatic men all partners from the last 6 months or the most recent sexual partner should be contacted
- Contacts of confirmed *Chlamydia* cases should be offered treatment prior to the results of their investigations being known (treat then test)
- A test of cure should be carried out following treatment.

***Chlamydia psittaci* (psittacosis)** also known as **parrot disease**, **parrot fever**, it is characterized by malaise, fever, myalgias and pneumonia. Exposure to an ill bird and a rash (Horder's spots) are pathognomonic. Erythromycin or tetracyclines are the drugs of choice.

Psittacosis (P is silent) = sittacosis = 6 causes
6 in Arabic is *sitta*

Urinary Tract Infection (UTI)

Asymptomatic bacteruria in pregnant women - treat with amoxicillin or cephalosporin

Lower urinary tract infections in women (cystitis)

- Local antibiotic guidelines should be followed if available
- Clinical knowledge summaries (CKS) recommend trimethoprim or nitrofurantoin for 3 days

Lower urinary tract infections in pregnancy

- Asymptomatic bacteriuria is screened for on the booking visit and should be treated with an antibiotic for 7 days (sensitivities should already be available)
- For acute lower urinary tract infections consider amoxicillin or an oral cephalosporin for 7 days*

For patients with sign of acute pyelonephritis hospital admission should be considered

- Local antibiotic guidelines should be followed if available
- The BNF currently recommends a broad-spectrum cephalosporin or a quinolone for 10-14 days
- Clinical knowledge summaries recommend ciprofloxacin for 7 days or co-amoxiclav for 14 days

*CKS also mention the use of trimethoprim and nitrofurantoin. Trimethoprim is a folate antagonist and concerns have been raised regarding the potential risk of neural tube defects. Manufacturers advise to avoid. Whilst short-term trimethoprim use is unlikely to cause folate deficiency it would seem reasonable to use an antibiotic such as amoxicillin first-line. Nitrofurantoin should be avoided at term because of the risk of neonatal hemolysis

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Congenital infections: the major congenital infections encountered in examinations are rubella, toxoplasmosis and cytomegalovirus

Cytomegalovirus is the most common congenital infection in the UK. Maternal infection is usually asymptomatic

	Rubella	Toxoplasmosis	Cytomegalovirus
Characteristic features	**Sensorineural deafness** Congenital cataracts Congenital heart disease (e.g. patent ductus arteriosus) Glaucoma	Cerebral calcification Chorioretinitis Hydrocephalus	**Growth retardation** **Purpuric skin lesions**
Other features	**Growth retardation** **Hepatosplenomegaly** **Purpuric skin lesions** 'Salt and pepper' chorioretinitis Microphthalmia **Cerebral palsy**	**Anemia** **Hepatosplenomegaly** **Cerebral palsy**	**Sensorineural deafness** Encephalitiis Pneumonitis **Hepatosplenomegaly** **Anemia** Jaundice **Cerebral palsy**

Toxoplasma Gondii is a protozoa which infects the body via the GI tract, lung or broken skin. Its oocysts release trophozoites which migrate widely around the body including to the eye, brain and muscle. The usual animal reservoir is the cat, although other animals such as rats carry the disease.

Most infections are asymptomatic. Symptomatic patients usually have a self-limiting infection, often having clinical features resembling infectious mononucleosis (fever, malaise, and lymphadenopathy). Other less common manifestations include meningioencephalitis and myocarditis.

Investigation for Toxoplasmosis

- Antibody test
- Sabin-Feldman dye test

Treatment is usually reserved for those with severe infections or patients who are immunosuppressed

- Pyrimethamine + Sulphadiazine for at least 6 weeks.

Congenital toxoplasmosis is due to transplacental spread from the mother. It causes a variety of effects to the unborn child including microcephaly, hydrocephalus, cerebral calcification and choroidoretinitis

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Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhea)

Travellers' diarrhea may be defined as at least 3 loose to watery stools in 24 hours with or without one or more of abdominal cramps, fever, nausea, vomiting or blood in the stool. The most common cause is *Escherichia coli*

***Bacillus cereus* infection most commonly results from reheated rice**

Another pattern of illness is 'acute food poisoning'. This describes the sudden onset of nausea, vomiting and diarrhea after the ingestion of a toxin. Acute food poisoning is typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*.

Stereotypical histories

Escherichia coli	**Common amongst travellers** Watery stools Abdominal cramps and nausea
Giardiasis	**Prolonged**, non-bloody **diarrhea**
Cholera	Profuse, watery diarrhea Severe dehydration resulting in weight loss Not common amongst travellers
Shigella	**Bloody diarrhea** Vomiting and abdominal pain
Staphylococcus aureus	Severe vomiting **Short incubation period**
Campylobacter	A flu-like prodrome Followed by crampy abdominal pains Fever and diarrhoea which may be bloody Complications include Guillain-Barre syndrome
Bacillus cereus	Two types of illness are seen Vomiting within 6 hours, stereotypically due to rice Diarrhoeal illness occurring after 6 hours (6-14hrs)
Amoebiasis	Gradual onset bloody diarrhea Abdominal pain and tenderness May last for several weeks

Incubation period

- 1-6 hrs: Staphylococcus aureus, Bacillus cereus
- 12-48 hrs: Salmonella, Escherichia coli
- 48-72 hrs: Shigella, Campylobacter
- > 7 days: Giardiasis, Amoebiasis

Cholera: is caused by Vibro cholerae - Gram negative bacteria

Features	Management
• Profuse 'rice water' diarrhoea • Dehydration • Hypoglycemia	• Oral rehydration therapy • Antibiotics: doxycycline, ciprofloxacin

Giardiasis is caused by the flagellate protozoan *Giardia lamblia*. It is spread by the faeco-oral route

Features

- Often asymptomatic
- Lethargy, bloating, abdominal pain
- Non-bloody diarrhoea
- Chronic/prolonged diarrhoea, malabsorption and lactose intolerance can occur
- Stool microscopy for trophozoite and cysts are classically negative, therefore **duodenal fluid aspirates or 'string tests'** (fluid absorbed onto swallowed string) are sometimes needed

Treatment is with metronidazole

Escherichia coli: a facultative anaerobic, lactose-fermenting, Gram negative rod which is a normal gut commensal.

E coli infections **lead to** a variety of diseases in humans including:

- Diarrhoeal illnesses
- UTIs
- Neonatal meningitis

E coli O157:H7 is a particular strain associated with severe, hemorrhagic, watery diarrhoea. It has a high mortality rate and can be complicated by hemolytic uremic syndrome. It is often spread by contaminated ground beef. The presentation is usually:

- **Diahrrea**
- **Renal Failure or Impairment**
- **Thrombocytopenia**
- **↓ Hb due to hemorrhage**

Salmonella group contains many members, most of which cause diarrhoeal diseases. They are aerobic, Gram negative rods which are not normally present as commensals in the gut.

Typhoid and paratyphoid are caused by *Salmonella typhi* and *Salmonella paratyphi* (types A, B & C) respectively. They are often termed enteric fevers, producing systemic symptoms such as headache, fever, and arthralgia.

Body louse is a vector (transmitter) of diseases. Body lice can spread epidemic typhus, trench fever, and louse-borne relapsing fever. Although louse-borne (epidemic) typhus is no longer widespread, outbreaks of this disease still occur during times of war, civil unrest, natural or man-made disasters, and in prisons where people live together in unsanitary conditions. Louse-borne typhus still exists in places where climate, chronic poverty, and social customs or war and social upheaval prevent regular changes and laundering of clothing

Features

- Initially systemic upset as above
- Relative bradycardia
- Abdominal pain, distension
- Constipation: although *Salmonella* is a recognised cause of diarrhoea, constipation is more common in typhoid
- Rose spots: present on the trunk in 40% of patients, and are more common in paratyphoid

Possible complications include

- Osteomyelitis (especially in sickle cell disease where *Salmonella* is one of the most common pathogens)
- GI bleed/perforation
- Meningitis
- Cholecystitis
- Chronic carriage (1%, more likely if adult ♀s)

Shigella:

- Causes bloody diarrhoea, abdo pain
- Severity depends on type: S sonnei (e.g. from UK) may be mild, S flexneri or S dysenteriae from abroad may cause severe disease
- Treat with ciprofloxacin

Pyrexia of Unkown Origin: defined as a prolonged fever of > 3 weeks which resists diagnosis after a week in hospital

Neoplasia	Infections	Connective tissue disorders
• Lymphoma • Hypernephroma • Preleukemia • Atrial myxoma	• Abscess • TB	

African Tick Typhus: caused by *Rickettsiae*.

Diagnosis:

- Black sopits on thigh
- Hx of tick bites
- Low grade fever
- Faint macular rash

Rocky Mountain Spotted Fever: is the most lethal and most frequently reported rickettsial infection, spreads by ticks, common in USA.

Presentation:

- Fever
- Rash on hands, feet which later → desequamte (peel)
- Tachycardia with no hypotension (unlike Staphylococcal Toxic Shock Syndrome)

Management: Doxycycline

Mediterranean Spotted Fever: (Boutonneuse fever) is a fever caused by the Rickettsia conorii and transmitted by the dog tick Rhipicephalus sanguineus.

- Incubation period: 7 days.
- The disease manifests abruptly with chills, **high fevers**, **myalgia** and joints pain, severe **headache**, photophobia and diarrhea.
- The location of the bite forms a **black spots or ulcerous crust** (tache noire). Around the fourth day of the illness an exanthem (**widespread rash**) appears, first macular and then maculopapular and sometimes petechial.
- Treated by Doxycycline.

Dengue fever is a type of viral hemorrhagic fever (also yellow fever, Lassa fever, Ebola)

Low platelet count and raised transaminase level is typical of dengue fever

Basics

- Transmitted by the Aedes aegyti mosquito
- Incubation period of 7 days
- A form of disseminated intravascular coagulation (DIC) known as dengue hemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

Features

- Causes headache (often retro-orbital)
- Myalgia
- Pleuritic pain
- Facial flushing (dengue)
- Maculopapular rash
- Pyrexia

Treatment is entirely symptomatic e.g. fluid resuscitation, blood transfusion etc

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Infectious mononucleosis (glandular fever) is caused by the Epstein-Barr virus (also known as human herpesvirus 4, HHV-4). It is most common in adolescents and young adults.

Features

- Sore throat
- Lymphadenopathy
- Pyrexia
- Malaise, anorexia, headache
- Palatal petechiae
- Splenomegaly - occurs in around 50% of patients and may rarely predispose to splenic rupture
- Hepatitis
- Presence of 50% lymphocytes with at least **10% atypical lymphocytes**
- Hemolytic anaemia

Management is supportive and includes:

- Rest during the early stages, drink plenty of fluid, avoid alcohol
- Simple analgesia for any aches or pains
- Consensus guidance in the UK is to avoid playing contact sports for 8 weeks after having glandular fever to reduce the risk of splenic rupture

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Malignancies associated with EBV infection:

- Burkitt's lymphoma*
- Hodgkin's lymphoma
- Nasopharyngeal carcinoma
- HIV-associated central nervous system lymphomas

The non-malignant condition hairy leukoplakia is also associated with EBV infection.

*EBV is currently thought to be associated with both African and sporadic Burkitt's

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Hepatitis E:

- RNA virus
- Spread by the faecal-oral route, incubation period = 3-8 weeks
- Common in Central and South-East Asia, North and West Africa, and in Mexico
- Causes a similar disease to hepatitis A, but carries a significant mortality (about 20%) during pregnancy
- Does not cause chronic disease
- A vaccine is currently in development, but is not yet in widespread use

H1N1 influenza (Swine Flu): outbreak was first observed in Mexico in early 2009. In June 2009, the WHO declared the outbreak to be a pandemic.

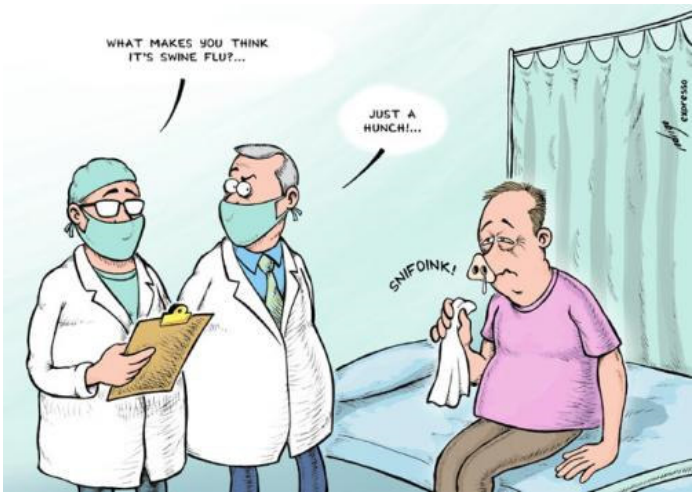
H1N1 virus is a subtype of the influenza A virus and the most common cause of flu in humans. The 2009 pandemic was caused by a new strain of the H1N1 virus.

The following groups are particularly at risk:

- Patients with chronic illnesses and those on immunosuppressants
- Pregnant women
- Young children under 5 years old

Features: the majority of symptoms are typical of those seen in a flu-like illness:

- Fever greater than 38ºC
- Myalgia
- Lethargy
- Headache
- Rhinitis
- Sore throat
- Cough
- Diarrhoea and vomiting
- A minority of patients may go on to develop an acute respiratory distress syndrome which may require ventilatory support.



Treatment: there are two main treatments currently available:

1. Oseltamivir (Tamiflu)
    - Oral medication
    - A neuraminidase inhibitor which prevents new viral particles from being released by infected cells
    - Common side-effects include nausea, vomiting, diarrhoea and headaches

2. Zanamivir (Relenza)
    - Inhaled medication*
    - Also a neuraminidase inhibitor
    - May induce bronchospasm in asthmatics

*intravenous preparations are available for patients who are acutely unwell

Parvovirus B19 is a DNA virus which causes a variety of clinical presentations. It was identified in the 1980's as the cause of erythema infectiosum

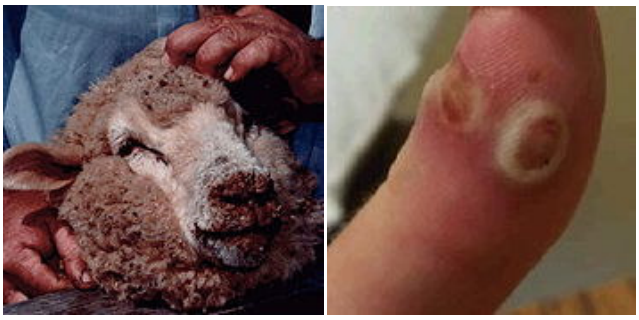
Erythema infectiosum (also known as fifth disease or 'slapped-cheek syndrome')

- Most common presenting illness
- Systemic symptoms: lethargy, fever, headache
- 'slapped-cheek' rash spreading to proximal arms and extensor surfaces

Other presentations

- Asymptomatic
- Pancytopenia in immunosuppressed patients
- Aplastic crises e.g. in sickle-cell disease (parvovirus B19 suppresses erythropoiesis for about a week so aplastic anemia is rare unless there is a chronic hemolytic anemia)

Orf is generally a condition found in sheep and goats although it can be transmitted to humans. It is caused by the parapox virus.



In animals

- 'scabby' lesions around the mouth and nose

In humans

- Generally affects the hands and arms
- Initially small, raised, red-blue papules
- Later may ↑ in size to 2-3 cm and become flat-topped and hemorrhagic

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Nematodes:

Ancylostoma braziliense

- Most common cause of cutaneous larva migrans
- Common in Central and Southern America

Strongyloides stercoralis

- Acquired percutaneously (e.g. Walking barefoot)
- Causes pruritus and larva currens - this has a similar appearance to cutaneous larva migrans but moves through the skin at a far greater rate
- Abdo pain, diarrhoea, pneumonitis
- May cause gram negative septicemia due to carrying of bacteria into bloodstream
- Eosinophilia sometimes seen
- Management: thiabendazole, albendazole. Ivermectin also used, particularly in chronic infections

Toxocara canis

- Commonly acquired by ingesting eggs from soil contaminated by dog faeces
- Commonest cause of visceral larva migrans
- Other features: eye granulomas, liver/lung involvement

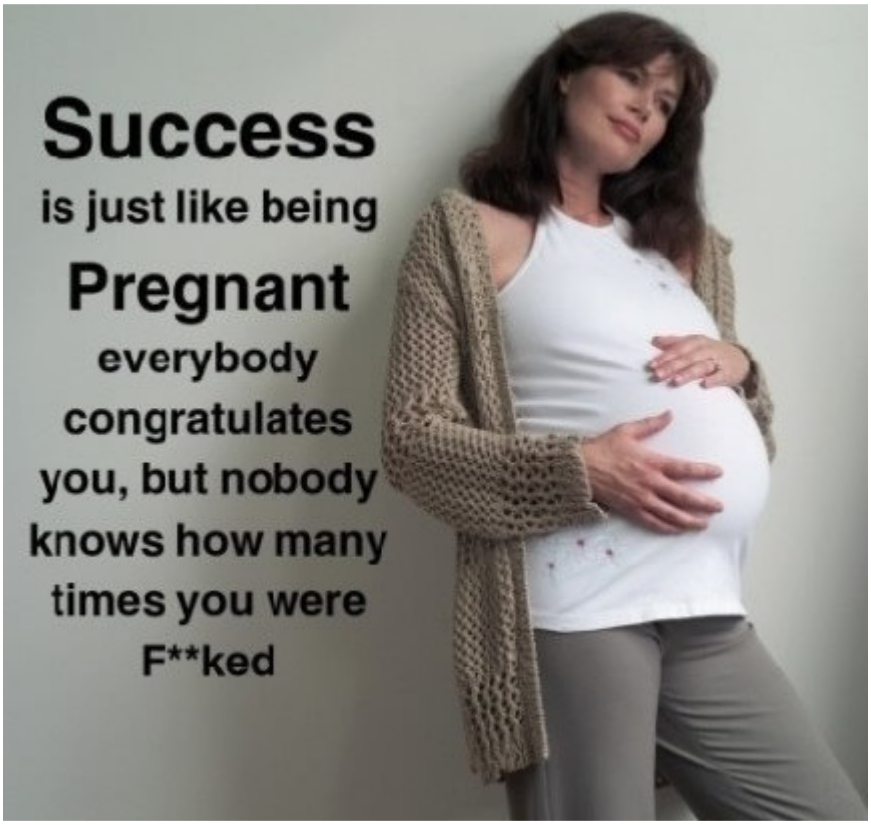
Tape worms are made up of repeated segments called proglottids. These are often present in faeces and are useful diagnostically

Cysticercosis	Hydatid disease
• Caused by Taenia solium (from pork) and Taenia saginata (from beef) • Management: niclosamide	• Caused by the dog tapeworm Echinococcus granulosus • Life-cycle involves dogs ingesting hydatid cysts from sheep liver • Often seen in farmers • May cause liver cysts • Management: albendazole

"Age? You mean now or when we first sat down?"

GYNE & OBS

Questions on maternal health during pregnancy are common in MRCP



Menstrual cycle may be divided into the following phases:

	Days
Menstruation	1-4
Follicular phase (proliferative phase)	5-13
Ovulation	14
Luteal phase (secretory phase)	15-28

LH surge causes ovulation

Further details are given in the table below

	Follicular phase (proliferative phase)	Luteal phase (secretory phase)
Ovarian histology	A number of follicles develop. One follicle will become dominant around the mid-follicular phase	Corpus luteum
Endometrial histology	Proliferation of endometrium	Endometrium changes to secretory lining under influence of progesterone
Hormones	A rise in FSH results in the development of follicles which in turn secrete oestradiol When the egg has matured; it secretes enough oestradiol to trigger the acute release of LH. This in turn leads to ovulation	Progesterone secreted by corpus luteum rises through the luteal phase. If fertilisation does not occur the corpus luteum will demise and progesterone levels fall Oestradiol levels also rise again during the luteal phase
Cervical mucus	Following menstruation the mucus is thick and forms a plug across the external os Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed spinnbarkeit	Under the influence of progesterone it becomes thick, scant, and tacky
Basal body temperature	Falls prior to ovulation due to the influence of oestradiol	Rises following ovulation in response to higher progesterone levels

Amenorrhoea may be divided into primary (failure to start menses by the age of 16 years) or secondary (cessation of established, regular menstruation for 6 months or longer).

Causes of primary amenorrhoea

- Turner's syndrome
- Testicular feminisation
- Congenital adrenal hyperplasia
- Congenital malformations of the genital tract

Causes of secondary amenorrhoea (after excluding pregnancy)

- Hypothalamic amenorrhoea (e.g. Stress, excessive exercise)
- Polycystic ovarian syndrome (PCOS)
- Hyperprolactinaemia
- Premature ovarian failure
- Thyrotoxicosis*

Initial investigations

- Exclude pregnancy with urinary or serum bHCG
- **Gonadotrophins: low levels indicate a hypothalamic cause where as raised levels suggest an ovarian problem (e.g. Premature ovarian failure)**
- Prolactin
- Androgen levels: raised levels may be seen in PCOS
- Oestradiol
- Thyroid function tests

*hypothyroidism may also cause amenorrhoea

Hypertension in pregnancy

The classification of hypertension in pregnancy is complicated and varies. Remember, in normal pregnancy:

- Blood pressure usually falls in the first trimester (particularly the diastolic), and continues to fall until 20-24 weeks
- After this time the blood pressure usually ↑ to pre-pregnancy levels by term

Hypertension in pregnancy in usually defined as:

- Systolic > 140 mmHg or diastolic > 90 mmHg
- Or an ↑ above booking readings of > 30 mmHg systolic or > 15 mmHg diastolic

After establishing that the patient is HTNsive they should be categorised into 1 of the following groups:

Pre-existing hypertension	Pregnancy-induced hypertension (PIH, gestational hypertension)	Pre-eclampsia
A history of hypertension before pregnancy or an elevated blood pressure > 140/90 mmHg before 20 weeks gestation No proteinuria, no edema Occurs in 3-5% of pregnancies and is more common in older women	Hypertension (as defined above) occurring in the second half of pregnancy (i.e. after 20 weeks) No proteinuria, no edema Occurs in around 5-7% of pregnancies Resolves following birth (typically after 1 month). Women with PIH are at ↑ risk of future pre-eclampsia or HTN later in life	Pregnancy-induced hypertension in association with proteinuria (> 0.3g / 24 hours) Edema may occur but is now less commonly used as a criteria Occurs in around 5% of pregnancies

Pre-eclampsia is a condition seen after 20 weeks gestation characterized by pregnancy-induced hypertension in association with proteinuria (> 0.3g / 24 hours). Edema used to be third element of the classic triad but is now often not included in the definition as it is not specific

Pre-eclampsia is important as it predisposes to the following problems **(complications)**

- Fetal: prematurity, intrauterine growth retardation
- Eclampsia
- Hemorrhage: placental abruption, intra-abdominal, intra-cerebral
- Cardiac failure
- Multi-organ failure

Risk factors

- > 40 years old
- Nulliparity (or new partner)
- Multiple pregnancy
- Body mass index > 30 kg/m^2
- Diabetes mellitus
- Pregnancy interval of more than 10 years
- Family history of pre-eclampsia
- Previous history of pre-eclampsia
- Pre-existing vascular disease such as hypertension or renal disease

There is some evidence to suggest that pre-eclampsia is actually less common in smokers

Features of **severe pre-eclampsia**

- Hypertension: typically > 170/110 mmHg and proteinuria as above
- Proteinuria: dipstick ++/+++
- Headache
- Visual disturbance
- Papilledema
- RUQ/epigastric pain
- Hyperreflexia
- Platelet count < 100 * 10^6/l, abnormal liver enzymes or HELLP syndrome

Management

- Consensus guidelines recommend treating blood pressure > 160/110 mmHg although many clinicians have a lower threshold
- Oral methyldopa is often used first-line with oral labetalol, nifedipine and hydralazine also being used
- For severe hypertension IV labetalol and IV hydralazine are used in addition to the above
- ACE inhibitors and angiotensin-2 receptor blockers should be avoided as they are teratogenic.
- Delivery of the baby is the most important and definitive management step. The timing depends on the individual clinical scenario

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Eclampsia may be defined as the development of seizures in association pre-eclampsia.

Magnesium sulphate - monitor reflexes + respiratory rate

Magnesium sulphate is used to both prevent seizures in patients with severe pre-eclampsia and treat seizures once they develop. Guidelines on its use suggest the following:

- Should be given once a decision to deliver has been made
- In eclampsia an IV bolus of 4g over 5-10 minutes should be given followed by an infusion of 1g/hour
- Urine output, reflexes, respiratory rate and oxygen saturations should be monitored during treatment
- Treatment should continue for 24 hours after last seizure or delivery (around 40% of seizures occur post-partum)

Other important aspects of treating severe pre-eclampsia/eclampsia include fluid restriction to avoid the potentially serious consequences of fluid overload

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HELLP syndrome is a life-threatening obstetric complication usually considered to be a variant of pre-eclampsia. Both conditions occur during the later stages of pregnancy, or sometimes after childbirth.

HELLP is an abbreviation of the main findings:

- **H**emolytic anemia
- **E**levated **L**iver enzymes and
- **L**ow **P**latelet count

Pregnancy: DVT/PE

Overview

- Pregnancy is a hypercoagulable state
- Majority occur in last trimester

Pathophysiology

- ↑ in factors VII, VIII, X and fibrinogen
- ↓ in protein S
- Uterus presses on IVC causing venous stasis in legs

Management

- Warfarin is contraindicated
- S/C low-molecular weight heparin preferred to IV heparin (less bleeding and thrombocytopenia)

Guidelines were published in 2007 by the Royal College of Obstetricians. Key points include:

- Chest x-ray should be performed in all patients

- compression duplex Doppler should be performed if the chest x-ray is normal - this may provide indirect evidence of a pulmonary embolism and negate the need for further radiation exposure

- The decision to perform a V/Q or CTPA should be taken at a local level after discussion with the patient and radiologist
- CTPA exposes the fetus to about 10-30% of the radiation dose of a V/Q scan
- V/Q scanning exposes the maternal breast tissue to less radiation than a CTPA

D-dimer is of no use in the investigation of thromboembolism as it ↑ in pregnancy

Cholestasis in Pregnancy:

Features:

- Seen across maternal ages and in both nulliparous and primiparous women
- More common in women with a history of cholestasis associated with OCP use and those who have a family history of cholestasis in pregnancy.
- Itching is the commonest symptom of cholestasis of pregnancy
- Severe jaundice is uncommon.
- Both ALT and Alk P are ↑.

Prognosis & Mangement:

- Long-term maternal outcome is good, although the risk of gallstones is ↑.
- The condition rapidly resolves after delivery of the child.
- Prior to delivery, antihistamines, benzodiazepines and ursodeoxycholic acid may all have a role to play in symptom relief

Peripartum Cardiomyopathy: is a dilated cardiomyopathy of uncertain aetiology occurring in the last month of pregnancy or within 6 months after delivery. Symptoms are the same as those of cardiac failure in non-pregnant patients.

Diagnosis:

- Absence of any other cause for the cardiac failure

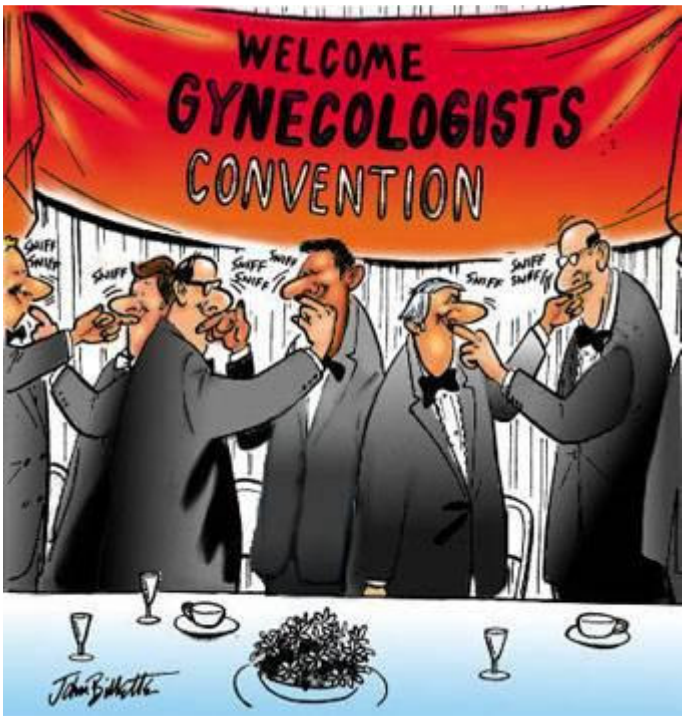
- Absence of heart disease before the last month of pregnancy
- Documented systolic dysfunction (echo)
- Biopsy is useless

Management:

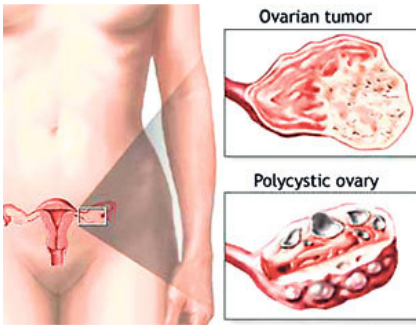
- Same as for cardiac failure, although ACE inhibitors should be avoide
- Mainstay of medical treatment is digoxin and loop diuretics. If indicated nitrates and inotropic support with dobutamine should be used.
- Heparin (during pregnancy) or Warfarin (postpartum) for the hypercoagulopathy (caused by cardiomyopathy + peripartum)
- Salt or Na^+ restriction

Prognosis:

- 50% recover to normal
- Recurrence is high in further pregnancies
- If no recovery, heart transplantation is needed



Polycystic ovarian syndrome (PCOS)



Is a complex condition of ovarian dysfunction thought to **affect between 5-20% of women of reproductive age**. Management is complicated and problem based. The aetiology of PCOS is not fully understood. Both hyperinsulinemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome

Features

- Subfertility and infertility
- Menstrual disturbances: oligomenorrhea and amenorrhoea
- Hirsuitism, acne (due to hyperandrogenism)
- Obesity
- Acanthosis nigricans (due to insulin resistance)

Investigations

- Pelvic ultrasound
- FSH, LH, prolactin, TSH, and testosterone are useful investigations: **raised LH:FSH ratio is a 'classical' feature** but is no longer thought to be useful is diagnosis. Prolactin may be normal or mildly elevated. **Testosterone** may be normal or mildly elevated - however, **if markedly raised consider other causes**
- Check for impaired glucose tolerance

Management:

General

- Weight reduction if appropriate
- If a women requires contraception then a combined oral contraceptive (COC) pill may help regulate her cycle and induce a monthly bleed (see below)

Hirsuitism and acne

- A COC pill may be used help manage hirsuitism. Possible options include a third generation COC which has fewer androgenic effects or co-cyprindiol which has an anti-androgen action. Both of these types of COC may carry an ↑ risk of venous thromboembolism
- If doesn't respond to COC then topical eflornithine may be tried
- Spironolactone, flutamide and finasteride may be used under specialist supervision

Infertility

- Weight reduction if appropriate
- The management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether metformin, clomifene or a combination should be used to stimulate ovulation
- A 2007 trial published in the New England Journal of Medicine suggested clomifene was the most effective treatment. There is a potential risk of multiple pregnancies with anti-estrogen* therapies such as clomifene
- Metformin is also used, either combined with clomifene or alone, particularly in patients who are obese
- Gonadotrophins

*work by occupying hypothalamic estrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion

Pelvic inflammatory disease (PID) is a term used to describe infection and inflammation of the ♀ pelvic organs including the uterus, fallopian tubes, ovaries and the surrounding peritoneum. It is usually the result of ascending infection from the endocervix

Causative organisms

- *Chlamydia trachomatis* - the most common cause
- *Neisseria gonorrhoeae*
- *Mycoplasma genitalium*
- Mycoplasma hominis

Features

- Lower abdominal pain
- Fever
- Deep dyspareunia
- Dysuria and menstrual irregularities may occur
- Vaginal or cervical discharge
- Cervical excitation

Investigation

- Screen for *Chlamydia* and Gonorrhoea

Management

- Due to the difficulty in making an accurate diagnosis, and the potential complications of untreated PID, consensus guidelines recommend having a low threshold for treatment
- Oral ofloxacin + oral metronidazole or intramuscular ceftriaxone + oral doxycycline + oral metronidazole
- RCOG guidelines suggest intrauterine contraceptive devices may be kept in in mild cases

Complications

- Infertility - the risk may be as high as 10-20% after a single episode
- Chronic pelvic pain
- Ectopic pregnancy

Breast Cancer: majority of breast cancer is sporadic. Familial breast cancer occurs in women with clustering of breast cancer, and includes those with both sporadic and genetic breast cancer. Some susceptibility genes for breast cancer have been identified. These include BRCA1, BRCA2, p53 and pTEN. Most genetic susceptibility however is as a consequence of as yet undetermined genes or those of low penetrance.

NICE issued guidelines in 2004 that set out the criteria for a **family history** that **suggests increased risk** of breast cancer and indicates referral to a specialist breast clinic. Increased risk of breast cancer is associated with at least one of the following in a family:

- Mother or sister diagnosed with breast cancer before the age of 40 years
- Close relatives from the same side of the family diagnosed with breast cancer at least one must be a mother, sister or daughter
- 3 close relatives diagnosed with breast cancer at any age

- Father or brother diagnosed with breast cancer at any age
- Mother or sister with breast cancer in both breasts (the first cancer diagnosed before the age of 50 years)
- 1 close relative with ovarian cancer and one with breast cancer, diagnosed at any age at least one must be a mother, sister or daughter.

Other risk factors for developing breast cancer include:

- Early NOT late menarche
- Late menopause
- Obesity
- Nulliparity
- Late pregnancy
- benign breast disease
- Oral contraceptives
- Hormone-replacement therapy
- Excess alcohol intake
- elevated insulin-like growth factor 1.

Ovarian cancer is the fifth most common malignancy in ♀s. The peak age of incidence is 60 years and it generally carries a poor prognosis due to late diagnosis. Around 90% of ovarian cancers are epithelial in origin.

Risk factors

- Family history: mutations of the BRCA1 or the BRCA2 gene
- Many ovulations: early menarche, late menopause, nulliparity

It is traditionally taught that infertility treatment ↑ the risk of ovarian cancer, as it ↑ the number of ovulations. Recent evidence however suggests that there is not a significant link. The combined oral contraceptive pill ↓ the risk (fewer ovulations) as does having many pregnancies.

Clinical features are notoriously vague

- Abdominal bloating
- Pelvic pain
- Urinary symptoms e.g. Urgency
- early satiety, bloating

Diagnosis is difficult and usually involves diagnostic laparotomy

---

Cervical Cancer:

Risk Factors: (Christiana is a poor lady who smoked cigarettes and became prostitute at a young age)

- Christians (male non-circumcision)
- Low socioeconomic status
- Smoking
- Multiple partners
- Commencement of sexual intercourse and/or pregnancy at young age
- Human papillomavirus (HPV), of course the 1st risk factor

Screening: Under the present UK Department of Health guidelines

- Women are sent their first invitation for routine screening at 25 years age.
- Then invited for screening every three years until the age of 49 years.
- From 50 to 64 years they are invited for screening every five years.
- Women who have had treatment for abnormal cells on the cervix may need to have a screening test more often.
- After 65 years no need to have cervical screening unless they have had recent cervical changes, or for some reason they have not had a screening test since the age of 50 years.

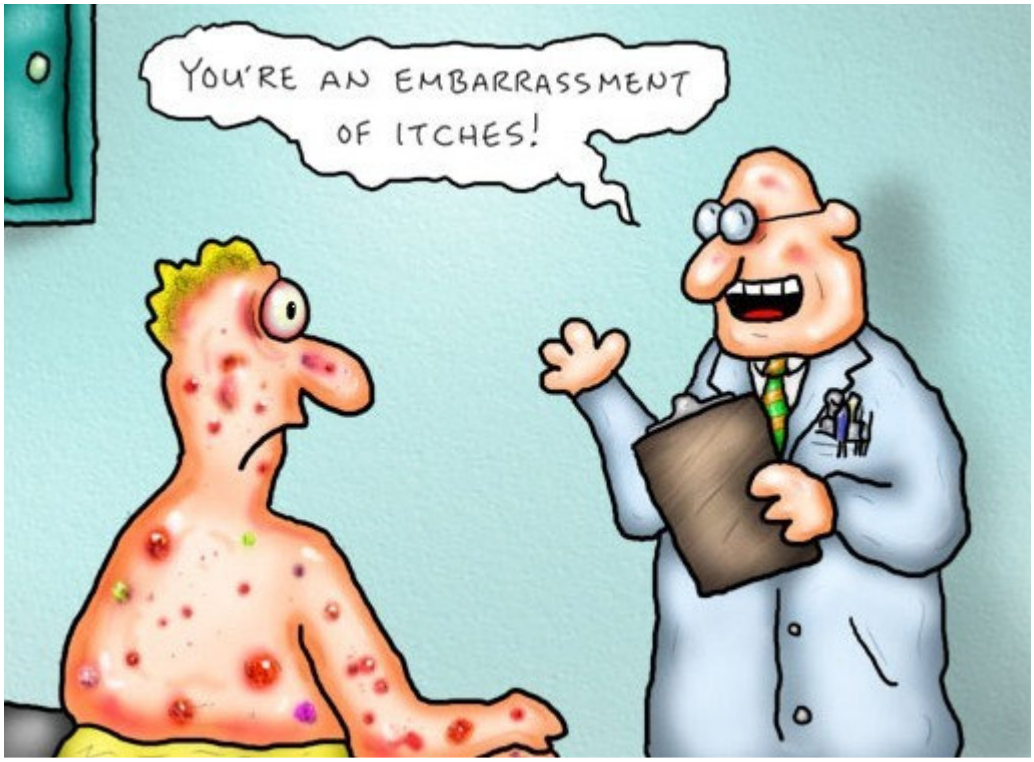
Common finding in cervical smear is **Dyskaryosis** or dysplasia refers to the precancerous change in cells. There are four types: borderline, mild, moderate and severe.

A smear result may also refer to CIN (**cervical intraepithelial neoplasia**); CIN1, CIN2, or CIN3 instead of mild, moderate or severe. This classification is not strictly accurate as CIN can only really be diagnosed with a biopsy.

Management:

- If the result shows mild cell changes or CIN1 → repeat smear in 6 months. Sometimes these slightly abnormal cells can go back to normal by themselves.
- If the next smear is abnormal, then referral is made for colposcopy.
- NHS guidelines: there should be 3 negative 6-monthly smears, before it is safe to go back to routine screening.
- Women with smears showing moderate or severe precancerous changes will be referred for colposcopy as they have a significant risk of proceeding to cervical cancer if left untreated.

DERMATOLOGY



Skin disorders associated with malignancy:

Skin disorder	Associated malignancies
Acanthosis nigricans	Gastric cancer
Acquired ichthyosis	Lymphoma
Erythroderma	Lymphoma
Acquired hypertrichosis lanuginosa	Gastrointestinal and lung cancer
Erythema gyratum repens	Lung cancer
Dermatomyositis	Bronchial and breast cancer
Migratory thrombophlebitis	Pancreatic cancer
Necrolytic migratory erythema	Glucagonoma
Pyoderma gangrenosum	Myeloproliferative disorders
Sweet's syndrome	Hematological Ca e.g. Myelodysplasia - tender, purple plaques
Tylosis	Oesophageal cancer

Skin disorders associated with pregnancy

Polymorphic eruption of pregnancy

- Pruritic condition associated with last trimester
- Lesions often first appear in abdominal striae
- Management depends on severity: emollients, mild potency topical steroids and oral steroids may be used

Pemphigoid gestationis

- Pruritic blistering lesions
- Often develop in peri-umbilical region, later spreading to the trunk, back, buttocks and arms
- Usually presents 2nd or 3rd trimester and is rarely seen in the first pregnancy
- Oral corticosteroids are usually required

Skin disorders associated with TB

Possible skin disorders

• Lupus vulgaris (accounts for 50% of cases) • Erythema nodosum • Scarring alopecia	• Scrofuloderma: breakdown of skin overlying a tuberculous focus • Verrucosa cutis • Gumma

Lupus vulgaris is the most common form of cutaneous TB seen in the Indian subcontinent. It generally occurs on the face and is common around the nose and mouth. The initial lesion is an erythematous flat plaque which gradually becomes elevated and may ulcerate later

Skin disorders associated with thyroid disease

Hypothyroidism	Hyperthyroidism
• Dry (anhydrosis), cold, yellowish skin • Non-pitting oedema (e.g. hands, face) • Dry, coarse scalp hair, loss of lateral aspect of eyebrows • Eczema • Xanthomata	• Pretibial myxoedema: erythematous, oedematous lesions above the lateral malleoli • Thyroid acropachy: clubbing • Scalp hair thinning • ↑ sweating

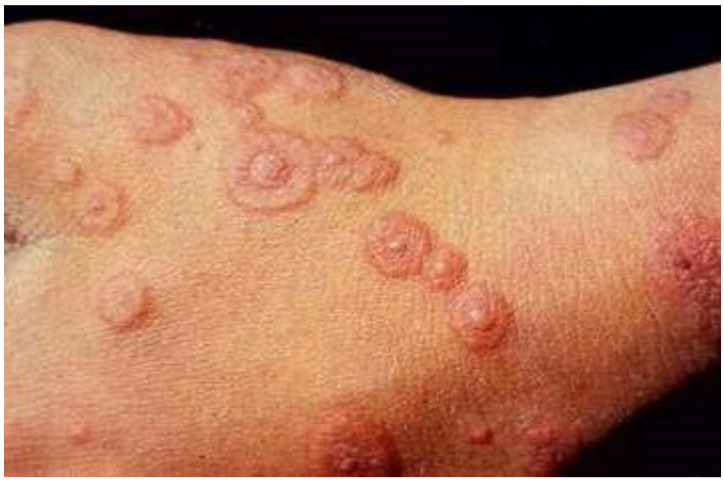
Pruritus can occur in both hyper- and hypothyroidism

Erythema multiforme:

- Target lesions (typically worse on peripheries e.g. Palms and soles)
- Severe = stevens-johnson syndrome (blistering and mucosal involvement)

Causes

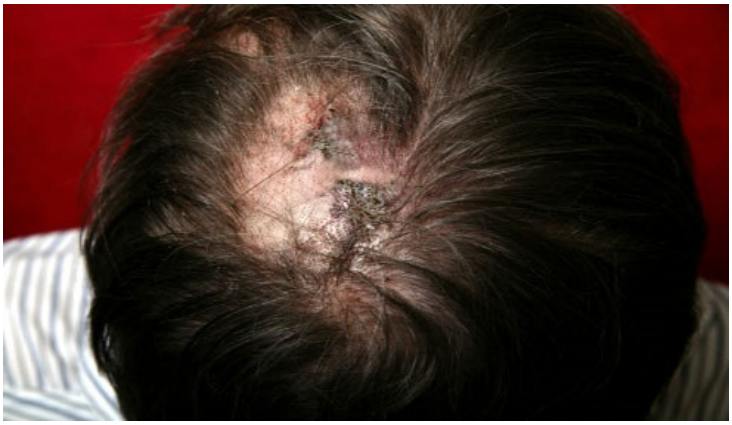
- Idiopathic
- Bacteria: mycoplasma, *Streptococcus*
- Viruses: **herpes simplex virus**, Orf
- Drugs: penicillin, sulphonamides, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill, nevirapine
- Connective tissue disease e.g. Systemic lupus erythematosus
- Sarcoidosis
- Malignancy



Alopecia may be divided into scarring (destruction of hair follicle) and non-scarring (preservation of hair follicle)

Scarring alopecia

- Trauma, burns
- Radiotherapy
- Lichen planus
- Discoid lupus
- Tinea capitis*
- TB



Non-scarring alopecia

- ♂-pattern baldness
- Drugs: cytotoxic drugs, carbimazole, heparin, oral contraceptive pill, colchicine
- Nutritional: iron and zinc deficiency
- Autoimmune: alopecia areata
- Telogen effluvium (hair loss following stressful period e.g. Surgery)
- Trichotillomania "hair loss from a patient's repetitive self-pulling of hair"

*scarring would develop in untreated tinea capitis if a kerion develops

Alopecia areata is a presumed autoimmune condition causing localised, well demarcated patches of hair loss. At the edge of the hair loss, there may be small, broken 'exclamation mark' hairs

Hair will regrow in 50% of patients by 1 year, and in 80-90% eventually. Careful explanation is therefore sufficient in many patients. Other treatment options include:

- Topical or intralesional corticosteroids
- Topical minoxidil
- Phototherapy
- Dithranol
- Contact immunotherapy
- Wigs

Shin lesions: The differential diagnosis of shin lesions includes the following conditions:

- Erythema nodosum
- Pretibial myxedema
- Pyoderma gangrenosum
- Necrobiosis lipoidica diabeticorum

Below are the characteristic features:

Erythema nodosum

- Symmetrical, erythematous, tender, nodules which heal without scarring
- Most common causes are streptococcal infections, sarcoidosis, inflammatory bowel disease and drugs (penicillins, sulphonamides, oral contraceptive pill)

Pretibial myxedema

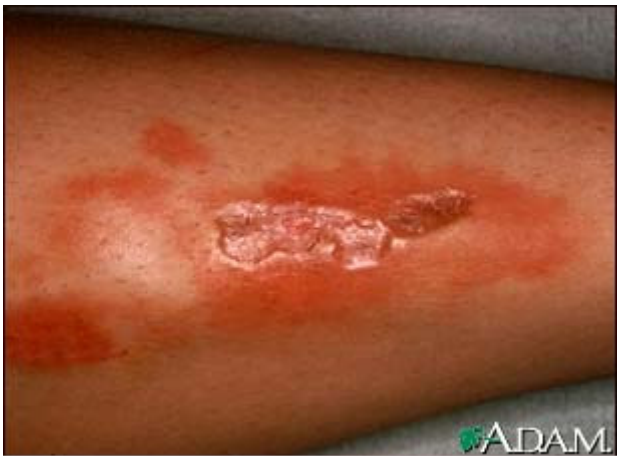
- symmetrical, erythematous lesions seen in Graves' disease
- shiny, orange peel skin

Pyoderma gangrenosum

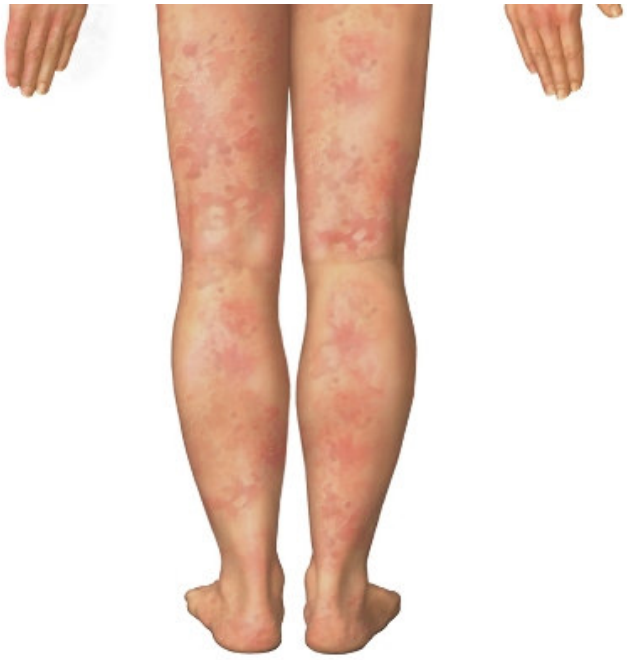
- Initially **small red papule**
- **Later deep, red, necrotic ulcers with a violaceous border**
- Idiopathic in 50%, may also be seen in inflammatory bowel disease, connective tissue disorders and myeloproliferative disorders

Necrobiosis lipoidica diabeticorum

- Shiny, painless areas of yellow/red skin typically on the shin of **diabetics**
- Often associated with telangiectasia



Erythema nodosum



Overview

- Inflammation of subcutaneous fat
- Typically causes tender, erythematous, nodular lesions
- Usually occurs over shins, may also occur elsewhere (e.g. Forearms, thighs)
- Usually resolves within 6 weeks
- Lesions heal without scarring

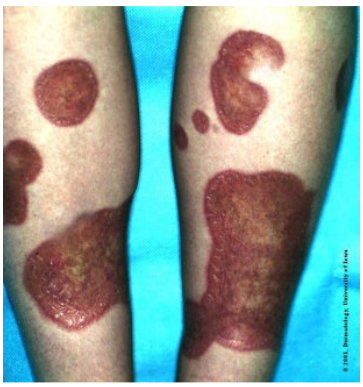
Causes

- Infection: streptococci, TB, brucellosis
- Systemic disease: sarcoidosis, inflammatory bowel disease, Behcet's
- Malignancy/lymphoma
- Drugs: penicillins, sulphonamides, combined oral contraceptive pill
- Pregnancy

Pyoderma Gangrenosum:

Features

- Typically on the lower limbs
- Initially small red papule
- Later deep, red, necrotic ulcers with a violaceous border
- May be accompanied systemic systems e.g. Fever, myalgia



Causes*

- Idiopathic in 50%
- IBD: ulcerative colitis, crohn's
- Rheumatoid arthritis, SLE
- Myeloproliferative disorders
- Lymphoma, myeloid leukemias
- Monoclonal gammopathy (IgA)
- Primary biliary cirrhosis

Management

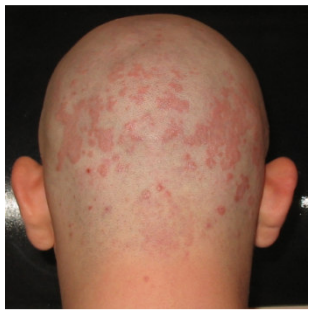
- The potential for rapid progression is high in most patients and whilst topical and intralesional steroids have a role in management most doctors advocate oral steroids as first-line treatment
- Other immunosuppressive therapy, for example Cyclosporin and infliximab, have a role in difficult cases

*note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is generally not included in a differential of potential causes

Seborrhoeic dermatitis in adults is a chronic dermatitis thought to be caused by an inflammatory reaction related to a proliferation of a normal skin inhabitant, a fungus called Malassezia (formerly known as Pityrosporum ovale). It is common, affecting around 2% of the general population. Seborrhoeic dermatitis is more common in patients with Parkinson's disease

Features

- Eczematous lesions on the sebum-rich areas: scalp (may cause dandruff), periorbital, auricular and nasolabial folds
- Otitis externa and blepharitis may develop



Associated conditions include

- HIV
- Parkinson's disease

Scalp disease management

- Over the counter preparations containing zinc pyrithione ('Head & Shoulders') and tar ('Neutrogena T/Gel') are first-line
- The preferred second-line agent is ketoconazole
- Selenium sulphide and topical corticosteroid may also be useful

Face and body management

- Topical antifungals: e.g. Ketoconazole
- Topical steroids: best used for short periods
- Difficult to treat - recurrences are common

Venous Ulceration is typically seen above the medial malleolus

Investigations

- Ankle-brachial pressure index (ABPI) is important in non-healing ulcers to assess for poor arterial flow which could impair healing
- A 'normal' ABPI may be regarded as between 0.9 - 1.2. Values below 0.9 indicate arterial disease. Interestingly, values above 1.3 may also indicate arterial disease, in the form of false-negative results secondary to arterial calcification (e.g. In diabetics)

Management

- Compression bandaging, usually four layer (only treatment shown to be of real benefit)
- Oral pentoxifylline (Trental®), a peripheral vasodilator, improves healing rate
- Small evidence base supporting use of flavinoids
- Little evidence to suggest benefit from hydrocolloid dressings, topical growth factors, ultrasound therapy and intermittent pneumatic compression

---

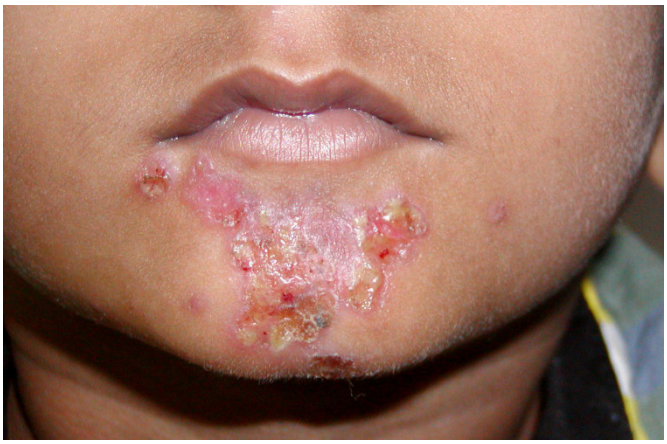
Malignant Melanoma: the invasion depth of a tumour (Breslow depth) is the single most important factor in determining prognosis of patients with malignant melanoma

Breslow Thickness	Approximate 5 year survival
< 1 mm	95-100%
1 - 2 mm	80-95%
2.1 - 4 mm	60-75%
> 4 mm	50%

Impetigo

Impetigo - topical fusidic acid → oral flucloxacillin / topical mupirocin

Clinical Knowledge Summaries recommend topical mupirocin as a second-line treatment for small areas of impetigo. Whilst it could be argued oral flucloxacillin should be used for unresponsive impetigo, recent hospital stay raises possibility that MRSA could be responsible



Limited, localised disease

- Topical fusidic acid is first-line
- Topical retapamulin is used 2nd-line if fusidin is ineffective or not tolerated
- MRSA is not susceptible to either fusidic acid or retapamulin. Topical mupirocin (Bactroban) should be used in this situation

Extensive disease

- Oral flucloxacillin
- Oral erythromycin if penicillin allergic

Erythema ab igne is a skin disorder caused by over exposure to infrared radiation. Characteristic features include erythematous patches with hyperpigmentation and telangiectasia. A typical history would be an elderly women who always sits next to an open fire (ovens)

If the cause is not treated then patients may go on to develop squamous cell skin cancer

---

Actinic keratoses, or solar, keratoses (AK) is a common premalignant skin lesion that develops as a consequence of chronic sun exposure

Features

- Small, crusty or scaly, lesions
- May be pink, red, brown or the same color as the skin
- Typically on sun-exposed areas e.g. Temples of head
- Multiple lesions may be present

Management options include

- Prevention of further risk: e.g. Sun avoidance, sun cream
- Fluorouracil cream: typically a 2 to 3 week course. The skin will become red and inflamed - sometimes topical hydrocortisone is given following fluorouracil to help settle the inflammation
- Topical diclofenac: may be used for mild AKs. Moderate efficacy but much fewer side-effects
- Topical imiquimod: trials have shown good efficacy
- Cryotherapy
- Curettage and cauter

Skin & DM

Note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is often not included in a differential of potential causes

- Necrobiosis lipoidica
    - Shiny, painless areas of yellow/red/brown skin typically on the shin
    - Often associated with surrounding telangiectasia
- Infection
    - Candidiasis
    - Staphylococcal
- Neuropathic ulcers
- Vitiligo
- Lipoatrophy
- Granuloma annulare*
    - Papular lesions that are often slightly hyperpigmented and depressed centrally

*it is not clear from recent studies if there is actually a significant association between diabetes mellitus and granuloma annulare, but it is often listed in major textbooks

LICHEN

- **P**lanus: **P**urple, **P**ruritic, **P**apular, **P**olygonal rash on flexor surfaces. Wickham's striae over surface. Oral involvement common
- Sclerosus: itchy white spots typically seen on the vulva of elderly women

Lichen Planus

Is a skin disorder of unknown etiology; most probably being **immune** mediated

Features

- Itchy, papular rash most common on the palms, soles, genitalia and flexor surfaces of arms
- Rash often polygonal in shape, 'white-lace' pattern on the surface (wickham's striae)
- Koebner phenomenon seen
- **Mucous membrane** involvement
- **Nails**: thinning of nail plate, longitudinal ridging

Lichenoid drug eruptions - causes:

- Gold
- Quinine
- Thiazides

Lichen Sclerosus

Was previously termed lichen sclerosus et atrophicus. It is an **inflammatory** condition which usually affects the **genitalia** and is more common in **elderly ♀s**. Lichen sclerosus leads to **atrophy of the epidermis** with white plaques forming

Features

- Itch is prominent

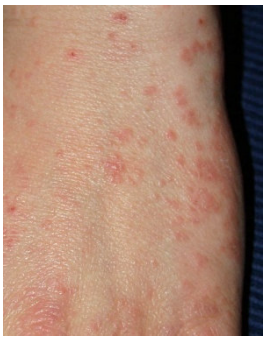
A biopsy is often performed to exclude other diagnoses

Management

- Topical steroids and emollients
- ↑ risk of vulval cancer

Scabies is caused by the mite Sarcoptes scabiei and is spread by prolonged skin contact. It typically affects children and young adults.

The scabies mite burrows into the skin, laying its eggs in the **stratum corneum**. The intense pruritus associated with scabies is due to a delayed type IV hypersensitivity reaction to mites/eggs which occurs about 30 days after the initial infection.



Features

- Widespread pruritus
- Linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist
- In infants the face and scalp may also be affected
- Secondary features are seen due to scratching: excoriation, infection

Management

- Permethrin 5% is first-line
- Malathion 0.5% is second-line
- Give appropriate guidance on use (see below)
- Pruritus persists for up to 4-6 weeks post eradication

Patient guidance on treatment (from Clinical Knowledge Summaries)

- Avoid close physical contact with others until treatment is complete
- All household and close physical contacts should be treated at the same time, even if asymptomatic
- Launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

The BNF advises to apply the insecticide to all areas, including the face and scalp, contrary to the manufacturer's recommendation. Patients should be given the following instructions:

- Apply the insecticide cream or liquid to cool, dry skin
- Pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow
- Allow to dry and leave on the skin for 8–12 hours for permethrin, or for 24 hours for malathion, before washing off
- Reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc
- Repeat treatment 7 days later

Psoriasis: Can be divided into type 1 and 2

Type 1

- Presents < 40 years old
- Positive family history
- Associated with HLA-CW6

Type 2

- Presents > 50 years old
- No family history

Features

- Red, scaly plaques
- Scalp, extensor surfaces elbows/knees, sacrum
- Nail signs: pitting, onycholysis
- Arthritis

Cause

- Abnormal T cell activity stimulates keratinocyte proliferation (rather than an actual primary keratinocyte disorder)
- Mediated by type 1 helper T cells

Management

Topical

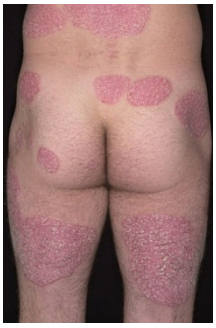
- Simple emollients
- Coal tar: probably inhibit DNA synthesis
- Topical corticosteroids: particularly flexural disease. Mild steroids are useful in facial psoriasis
- Calcipotriol: vitamin D analogue which ↓ epidermal proliferation and restores a normal horny layer
- Dithranol: inhibits DNA synthesis, wash off after 30 mins, SE: burning, staining

Flexural psoriasis

- emollients
- topical steroids

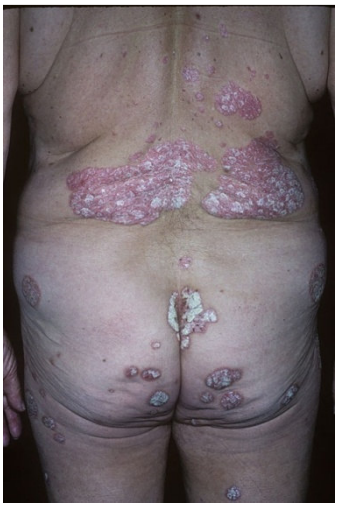
Phototherapy

- Narrow band ultraviolet B light (311-313nm) is now the treatment of choice
- Photochemotherapy is also used - psoralen + ultraviolet A light (PUVA)
- Adverse effects: skin ageing, squamous cell cancer (not melanoma)



Factors may exacerbate psoriasis:

- Trauma
- Alcohol
- drugs: β blockers, lithium, antimalarials (chloroquine and hydroxychloroquine), NSAIDs and ACE inhibitors
- Systemic steroids withdrawal



Scalp psoriasis

- Calcipotriol lotion
- Steroid lotion + shampoo
- Combination shampoo: betamethasone with vitamin D analogues
- Coconut oil compound shampoos (combination of coal tar, salicylic acid and sulphur)
- Tar shampoo

Systemic therapy

- Methotrexate: useful if associated joint disease
- Biological agents: infliximab, etanercept and adalimumab, Ustekinumab (IL-12 and IL-23 blocker) is showing promise in early trials.
- Cyclosporin
- Systemic retinoids

Guttate psoriasis is more common in children and adolescents. It may be precipitated by a streptococcal infection (tonsillitis) 2-4 weeks prior to the lesions appearing

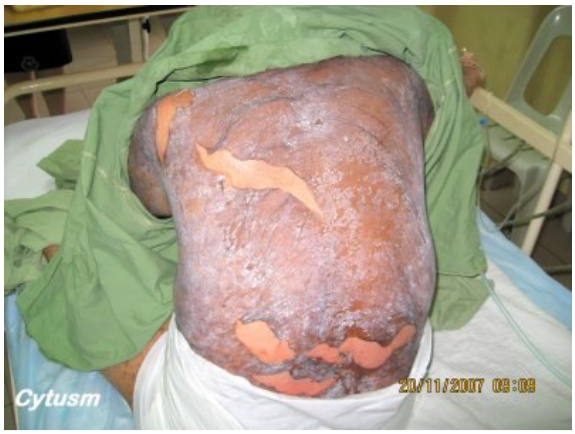
Features

- Tear drop papules on the trunk and limbs

Management

- Most cases resolve spontaneously within 2-3 months
- There is no firm evidence to support the use of antibiotics to eradicate streptococcal infection
- Topical agents as per psoriasis
- UVB phototherapy
- Tonsillectomy may be necessary with recurrent episodes

Toxic Epidermal Necrolysis (TEN) A potentially life-threatening skin disorder that is mostly seen secondary to a drug reaction. In this condition the skin develops a scalded appearance over an extensive area. Some authors consider TEN to be the severe end of a spectrum of skin disorders which includes erythema multiforme and Stevens-Johnson syndrome



Features

- Systemically unwell e.g. Pyrexia, tachycardic
- Positive Nikolsky's sign: the epidermis separates with mild lateral pressure

Management

- Stop precipitating factor
- Supportive care, often in intensive care unit
- Intravenous immunoglobulin has been shown to be effective and is now commonly used first-line
- Other treatment options include: immunosuppressive agents (Cyclosporin and cyclophosphamide), plasmapheresis

Drugs known to induce TEN

- Phenytoin
- Sulphonamides
- Allopurinol
- Penicillins
- Carbamazepine
- NSAIDs

Keloid scars are tumour-like lesions that arise from the connective tissue of a scar and extend beyond the dimensions of the original wound

Predisposing factors

- More common in young, black, male adults, rare in the elderly
- Common sites (in order of decreasing frequency): sternum, shoulder, neck, face, extensor surface of limbs, trunk
- Keloid scars are less likely if incisions are made along relaxed skin tension lines*

Treatment

- Early keloids may be treated with intra-lesional steroids e.g. Triamcinolone
- Excision is sometimes required

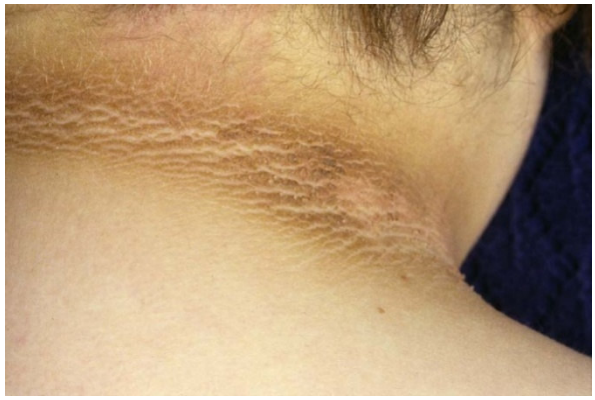
*Langer lines were historically used to determine the optimal incision line. They were based on procedures done on cadavers but have been shown to produce worse cosmetic results than when following skin tension lines

---

Acanthosis nigricans: describes symmetrical, brown, velvety plaques that are often found on the neck, axilla and groin

Causes

- Internal malignancy (esp. Gastrointestinal)
- Insulin-resistant diabetes mellitus
- Obesity
- Acromegaly
- Cushing's disease
- Hypothyroidism
- Polycystic ovarian syndrome
- Familial
- Prader-Willi syndrome
- Drugs: oral contraceptive pill, Nicotinic acid

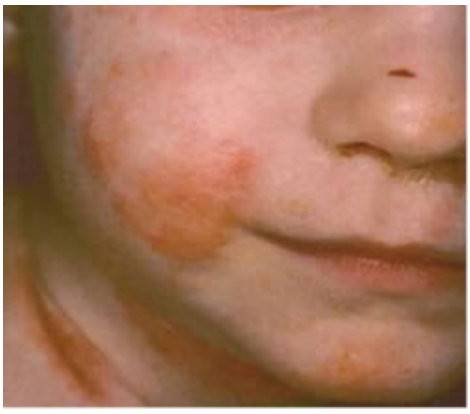


Eczema:

Diagnosis

UK Working Party Diagnostic Criteria for Atopic Eczema
An itchy skin condition in the last 12 months
Plus three or more of

- Onset below age 2 years*
- History of flexural involvement**
- History of generally dry skin
- Personal history of other atopic disease***
- Visible flexural dermatitis



*not used in children under 4 years
**or dermatitis on the cheeks and/or extensor areas in children aged 18 months or under
***in children aged under 4 years, history of atopic disease in a first degree relative may be included

Management:

Topical steroids
- moderate: Clobetasone butyrate 0.05%
- potent: Betamethasone valerate 0.1%
- very potent: Clobetasol propionate 0.05%

Use weakest steroid cream which controls patient's symptoms

The table below shows topical steroids by potency

Mild	Moderate	Potent	Very potent
Hydrocortisone 0.5-2.5%	Betamethasone valerate 0.025% (Betnovate RD) Clobetasone butyrate 0.05% (Eumovate)	Betamethasone dipropionate 0.025% (Propaderm) Betamethasone valerate 0.1% (Betnovate)	Clobetasol propionate 0.05% (Dermovate)

Finger tip rule
- 1 finger tip unit (FTU) = 0.5g, sufficient to treat area about twice that of flat adult hand

Topical steroid doses for eczema in adults

Area of skin	Fingertip units per dose
Hand and fingers (front and back)	1.0
A foot (all over)	2.0
Face and neck	2.5
An entire arm and hand	4.0
Front of chest and abdomen	7.0
Back and buttocks	7.0
An entire leg and foot	8.0

Pompholyx is a type of eczema which affects both the hands (cheiropompholyx) and the feet (pedopompholyx). It is also known as dyshidrotic eczema

Features
- Small blisters on the palms and soles
- Pruritic, sometimes burning sensation
- Once blisters burst skin may become dry and crack

Management
- Cool compresses
- Emollients
- Topical steroids

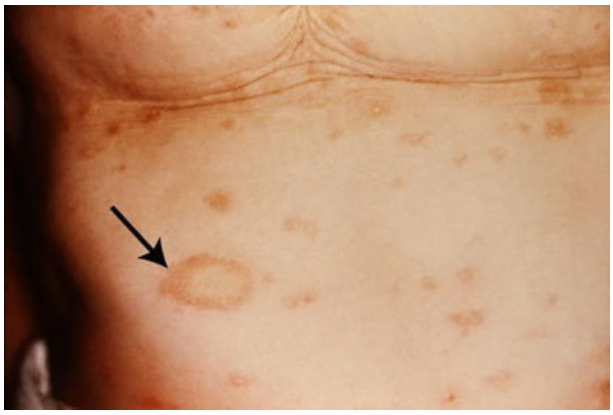
Pityriasis rosea

Overview

- Cause unknown, herpes hominis virus 7 (HHV-7) is a possibility
- Tends to affect young adults

Features

- Herald patch (usually on trunk)
- Followed by erythematous, oval, scaly patches which follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance



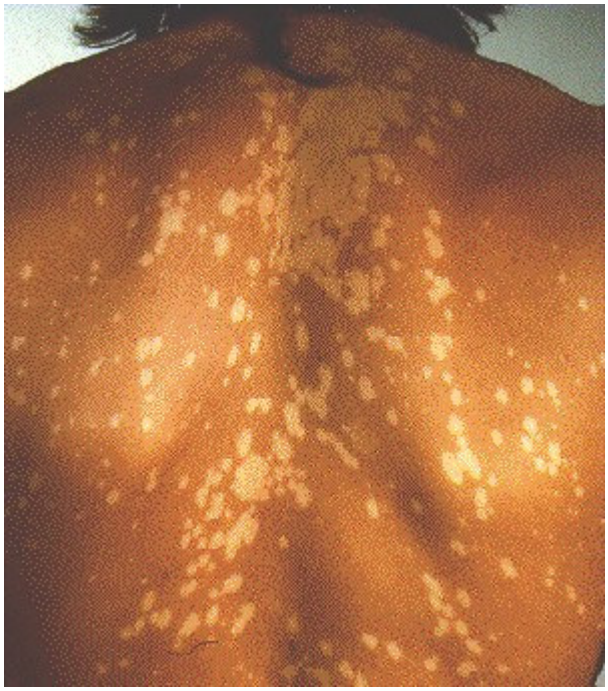
Management

- Self-limiting, usually disappears after 4-6 weeks

Pityriasis Versicolor, also called tinea versicolor, is a superficial cutaneous fungal infection caused by Malassezia furfur (formerly termed Pityrosporum ovale)

Features

- Most commonly affects trunk
- Patches may be hypopigmented, pink or brown (hence versicolor)
- Scale is common
- Mild pruritus



Predisposing factors

- Occurs in healthy individuals
- Immunosuppression
- Malnutrition
- Cushing's

Management

- Topical antifungal e.g. Terbinafine or selenium sulphide
- If extensive disease or failure to respond to topical treatment then consider oral itraconazole

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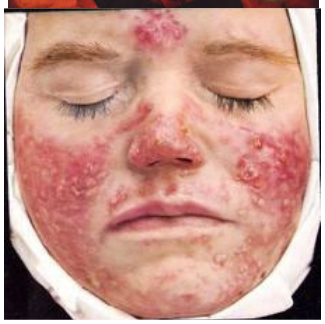
Acne Rosacea is a chronic skin disease of unknown aetiology



Features

- Typically affects nose, cheeks and forehead
- Flushing is often first symptom
- Telangiectasia are common
- Later develops into persistent erythema with papules and pustules
- Rhinophyma
- Ocular involvement: blepharitis

Management

- Topical metronidazole may be used for mild symptoms (i.e. Limited number of papules and pustules, no plaques)
- More severe disease is treated with systemic antibiotics e.g. Oxytetracycline
- Recommend daily application of a high-factor sunscreen
- Camouflage creams may help conceal redness
- Laser therapy may be appropriate for patients with prominent telangiectasia

---

Acne vulgaris is a common skin disorder which usually occurs in adolescence. It typically affects the face, neck and upper trunk and is characterized by the obstruction of the pilosebaceous follicle with keratin plugs which results in comedones, inflammation and pustules.

Epidemiology

- Affects around 80-90% of teenagers, 60% of whom seek medical advice
- Acne may also persist beyond adolescence, with 10-15% of ♀s and 5% of ♂s over 25 years old being affected

Pathophysiology is multifactorial

- Follicular epidermal hyperproliferation resulting in the formation of a keratin plug. This in turn causes obstruction of the pilosebaceous follicle. Activity of sebaceous glands may be controlled by androgen, although levels are often normal in patients with acne
- Colonisation by the anaerobic bacterium propionibacterium acnes
- Inflammation

Acne may be **classified** into mild, moderate or severe:

- Mild: open and closed comedones with or without sparse inflammatory lesions.
- Moderate acne: widespread non-inflammatory lesions and numerous papules and pustules
- Severe acne: extensive inflammatory lesions, which may include nodules, pitting, and scarring

A simple step-up **management** scheme often used in the treatment of acne is as follows:

- Single topical therapy (topical retinoids, benzyl peroxide)
- Topical combination therapy (topical antibiotic, benzoyl peroxide, topical retinoid)
- Oral antibiotics: e.g. Oxytetracycline, doxycycline. Improvement may not be seen for 3-4 months. Minocycline is now considered second line treatment due to the possibility of irreversible pigmentation. Gram negative folliculitis may occur as a complication of long-term antibiotic use - high-dose oral trimethoprim is effective if this occurs
- Oral isotretinoin: only under specialist supervision

(There is no role for dietary modification in patients with acne)

Isotretinoin is an oral retinoid used in the treatment of severe acne. Two-thirds of patients have a long term remission or cure following a course of oral isotretinoin

Adverse effects

- Teratogenicity: ♀s MUST be using two forms of contraception (e.g. Combined oral contraceptive pill and condoms)
- Dry skin, eyes and lips: the most common side-effect of isotretinoin
- Nose bleeds (caused by dryness of the nasal mucosa)
- Low mood
- Raised triglycerides
- Hair thinning
- Benign intracranial hypertension: isotretinoin treatment should not be combined with tetracyclines for this reason

Zinc deficiency

Features

- Perioral dermatitis: red, crusted lesions
- Acrodermatitis
- Alopecia
- Short stature
- Hypogonadism
- Hepatosplenomegaly
- Geophagia (ingesting clay/soil)
- Cognitive impairment

Koebner phenomenon describes skin lesions which appear at the site of injury. It is seen in:

- Psoriasis
- Vitiligo
- Warts
- Lichen planus
- Lichen sclerosus
- Molluscum contagiosum

Café-au-lait spots: Hyperpigmented lesions that vary in color from light brown to dark brown, with borders that may be smooth or irregular

Causes:

- Neurofibromatosis type I & II
- Tuberous sclerosis
- Fanconi anemia
- Mccune-Albright syndrome

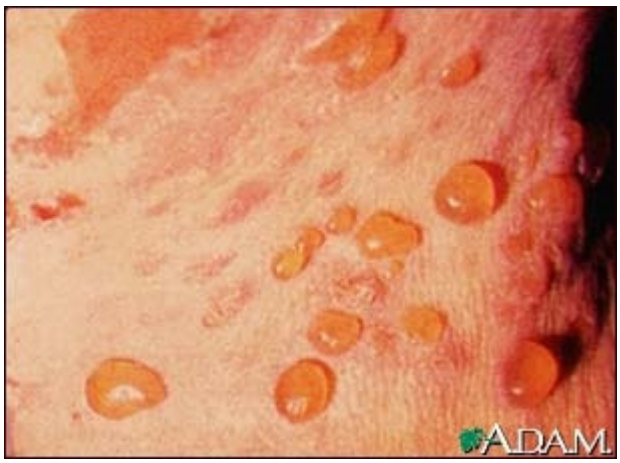
Bullous disorders causes of skin bullae:

- Congenital: epidermolysis bullosa
- Autoimmune: bullous pemphigoid, pemphigus
- Insect bite, Trauma, friction
- Drugs: barbiturates, furosemide

Bullous pemphigoid is an autoimmune condition causing sub-epidermal blistering of the skin. This is secondary to the development of antibodies against hemidesmosomal proteins BP180 and BP230

Bullous pemphigoid is more common in elderly patients. **Features** include

- Itchy, tense blisters typically around flexures
- Mouth is usually spared



Skin biopsy

- Immunofluorescence shows IgG and C3 at the dermoepidermal junction

Management

- Referral to dermatologist for biopsy and confirmation of diagnosis
- Oral corticosteroids are the mainstay of treatment
- Topical corticosteroids, immunosuppressants and antibiotics are also used

---

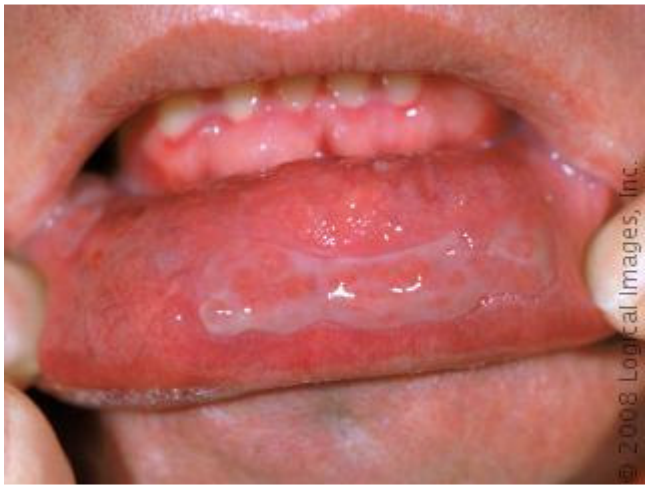
Pemphigus vulgaris is an autoimmune disease caused by antibodies directed against desmoglein, a cadherin-type epithelial cell adhesion molecule. It is more common in the Ashkenazi Jewish population

Blisters/bullae

- No mucosal involvement: bullous pemphigoid
- Mucosal involvement: pemphigus vulgaris

Features

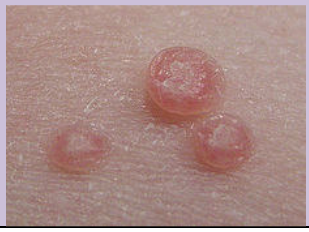
- Mucosal ulceration is common and often the presenting symptom. Oral involvement is seen in 50-70% of patients
- Skin blistering - flaccid, easily ruptured vesicles and bullae. Lesions are typically painful but not itchy. These may develop months after the initial mucosal symptoms. Nikolsky's describes the spread of bullae following application of horizontal, tangential pressure to the skin
- Acantholysis on biopsy



Management

- Steroids
- Immunosuppressants

Molluscum contagiosum: caused by poxvirus, common in immunocompermised patients, flesh-white or colored, dome-shaped, and pearly in appearance. They are often 1–5 millimeters in diameter, with a dimpled center. They are generally not painful, but they may itch or become irritated. Picking or scratching the bumps may lead to further infection or scarring.



Dermatitis herpetiformis - caused by IgA deposition in the dermis

Dermatitis herpetiformis is an autoimmune blistering skin disorder associated with coeliac disease. **It is caused by deposition of IgA in the dermis**.

Features	Diagnosis	Management
itchy, vesicular skin lesions on the extensor surfaces (e.g. Elbows, knees buttocks)	skin biopsy: direct immunofluorescence shows deposition of IgA in a granular pattern in the upper dermis	Gluten-free diet Dapsone

Contact dermatitis: there are two main types of contact dermatitis

- Irritant contact dermatitis: common - non-allergic reaction due to weak acids or alkalis (e.g. Detergents). Often seen on the hands. Erythema is typical, crusting and vesicles are rare
- Allergic contact dermatitis: type IV hypersensitivity reaction. Uncommon - often seen on the head following hair dyes. Presents as an acute weeping eczema which predominately affects the margins of the hairline rather than the hairy scalp itself. Topical treatment with a potent steroid is indicated

Cement is a frequent cause of contact dermatitis. The alkaline nature of cement may cause an irritant contact dermatitis whilst the dichromates in cement also can cause an allergic contact dermatitis

Nickel Dermatitis: is a common cause allergic contact dermatitis and is an example of a type IV hypersensitivity reaction. It is often caused by jewellery such as watches. It is diagnosed by a skin patch test

Porphyria Cutanea Tarda is the most common hepatic porphyria. It is due to an inherited defect in uroporphyrinogen decarboxylase or caused by hepatocyte damage e.g. alcohol, estrogens

Features

- Classically presents with photosensitive rash with **blistering** and **skin fragility** on the **face** and dorsal aspect of **hands** (most common feature)
- **Hypertrichosis**
- **Hyperpigmentation**

Investigations:

- Urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp

Management

- Chloroquine
- Venesection

Keratoacanthoma is a benign epithelial tumour. They are more frequent in middle age and do not become more common in old age (unlike basal cell and squamous cell carcinoma)

Features - said to look like a volcano or crater

- Initially a smooth dome-shaped papule
- Rapidly grows to become a crater centrally-filled with keratin

Spontaneous regression of keratoacanthoma within 3 months is common, often resulting in a scar. Such lesions should however be urgently excised as it is difficult clinically to exclude squamous cell carcinoma. Removal also may prevent scarring.

Granuloma annulare

- Papular lesions that are often slightly hyperpigmented and depressed centrally
- Typically occur on the dorsal surfaces of the hands and feet, and on the extensor aspects of the arms and legs

A number of associations have been proposed to conditions such as diabetes mellitus but there is only weak evidence for this

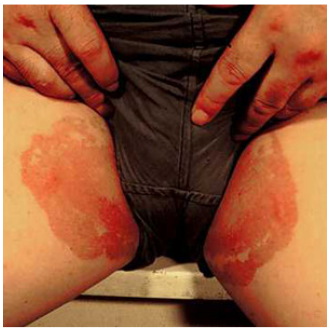
Erythroderma is a term used when more than 95% of the skin is involved in a rash of any kind

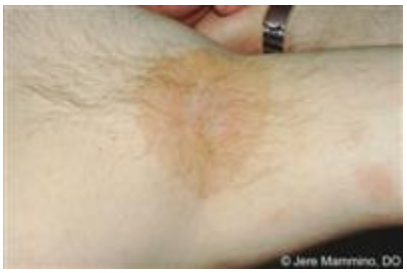
Causes of erythroderma

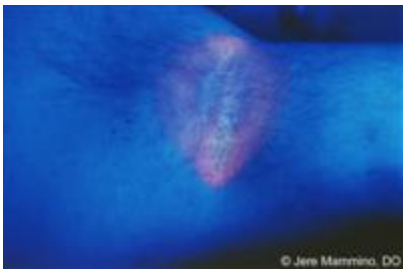
- Eczema
- Psoriasis
- Drugs e.g. Gold
- Lymphoma, leukemia
- Idiopathic

Erythrodermic psoriasis
• May result from progression of chronic disease to an exfoliative phase with plaques covering most of the body. Associated with mild systemic upset • More serious form is an acute deterioration. This may be triggered by a variety of factors such as withdrawal of systemic steroids. Patients need to be admitted to hospital for management

Erythrasma is a generally asymptomatic, flat, slightly scaly, pink or brown rash usually found in the groin or axillae. It is caused by an overgrowth of the diphtheroid Corynebacterium minutissimum







Examination with Wood's light reveals a coral-red fluorescence

Topical miconazole or antibacterial are usually effective. Oral erythromycin may be used for more extensive infection

Photosensitive skin disorders diseases aggravated by exposure to sunlight:

- Systemic lupus erythematosus, discoid lupus
- Porphyria (not acute intermittent)
- Herpes labialis (cold sores)
- Pellagra
- Xeroderma pigmentosum
- Solar urticaria
- Polymorphic light eruption

Tinea is a term given to dermatophyte fungal infections. Three main types of infection are described depending on what part of the body is infected

- Tinea capitis - scalp
- Tinea corporis - trunk, legs or arms
- Tinea pedis - feet

Tinea capitis (scalp ringworm)	Tinea corporis	Tinea pedis (athlete's foot)
• A cause of scarring alopecia mainly seen in children • Most common cause is trichophyton tonsurans in the UK and the USA • May also be caused by microsporum canis acquired from cats or dogs • Diagnosis: lesions due to microsporum canis green fluorescence under wood's *	• Causes include Trichophyton rubrum (also causes fungal nail infection) and Trichophyton verrucosum (e.g. From contact with cattle) • Well-defined annular, erythematous lesions with pustules and papules • May be treated with oral fluconazole	• Characterized by itchy, peeling skin between the toes • Common in adolescence

*lesions due to Trichophyton species do not readily fluoresce under Wood's lamp

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Stevens-Johnson syndrome severe form of erythema multiforme associated with mucosal involvement and systemic symptoms

Features

- Rash is typically maculopapular with target lesions being characteristic. May develop into vesicles or bullae
- Mucosal involvement
- Systemic symptoms: fever, arthralgia

Causes

- Idiopathic
- Bacteria: mycoplasma, *streptococcus*
- Viruses: herpes simplex virus, orf
- Drugs: penicillin, sulphonamides, carbamazepine, allopurinol, nsaids, oral contraceptive pill
- Connective tissue disease e.g. Sle
- Sarcoidosis
- Malignancy

Pruritus

The table below lists the main characteristics of the most important causes of pruritus:

Liver disease	History of alcohol excess Stigmata of chronic liver disease: spider naevi, bruising, palmar erythema, gynaecomastia etc Evidence of decompensation: ascites, jaundice, encephalopathy
Iron deficiency anemia	Pallor Other signs: koilonychia, atrophic glossitis, post-cricoid webs, angular stomatitis
Polycythemia	Pruritus particularly after warm bath 'Ruddy complexion' Gout Peptic ulcer disease
Chronic kidney disease	Lethargy & pallor Edema & weight gain Hypertension
Lymphoma	Night sweats Lymphadenopathy Splenomegaly, hepatomegaly Fatigue

Other causes:

- Hyper- and hypothyroidism
- Diabetes
- Pregnancy
- 'Senile' pruritus
- Urticaria
- Skin disorders: eczema, scabies, psoriasis, pityriasis rosea

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Hirsuitism & Hypertrichosis: hirsuitism is often used to describe androgen-dependent hair growth in women, with hypertrichosis being used for androgen-independent hair growth

Causes of hirsuitism	Causes of hypertrichosis
• Polycystic ovarian syndrome • Cushing's syndrome • Congenital adrenal hyperplasia • Androgen therapy • Adrenal tumour • Androgen secreting ovarian tumour • **Drugs: phenytoin**	• Drugs: minoxidil, **Cyclosporin**, diazoxide • Congenital hypertrichosis lanuginosa, congenital hypertrichosis terminalis • Porphyria cutanea tarda • Anorexia nervosa • GI and Lung malignancies.

Assessment of hirsuitism

- Ferriman-Gallwey scoring system: 9 body areas are assigned a score of 0 - 4, a score > 15 is considered to indicate moderate or severe hirsutism

Management of hirsuitism

- Advise weight loss if overweight
- Cosmetic techniques such as waxing/bleaching - not available on the NHS

- Consider using combined oral contraceptive pills such as co-cyprindiol (Dianette) or ethinylestradiol and drospirenone (Yasmin). Co-cyprindiol should not be used long-term due to the increased risk of venous thromboembolism
- Facial hirsuitism: topical eflornithine - contraindicated in pregnancy and breast-feeding

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Yellow nail syndrome: Slowing of nail growth leads to the characteristic thickened and discolored nails seen in yellow nail syndrome

Associations:

- Congenital lymphedema
- Pleural effusions
- Bronchiectasis
- Chronic sinus infections

Fungal nail infections

Onychomycosis is fungal infection of the nails.

Causes	Features	Investigation
• Dermatophytes - mainly Trichophyton rubrum, 90% of cases • Yeasts - such as *Candida* • Non-dermatophyte moulds	• 'Unsightly' nails are a common reason for presentation • Thickened, rough, opaque nails are the most common finding	• Nail clippings • Scrapings of the affected nail

Management

- Treatment is successful in around 50% of people
- Diagnosis should be confirmed by microbiology before starting treatment
- Dermatophyte infection: oral terbinafine is currently recommended first-line with oral itraconazole as an alternative. Six weeks therapy is needed for fingernail infections whilst toenails should be treated for 12 weeks
- *Candida* infection: mild disease should be treated with topical antifungals (e.g. Amorolfine) whilst more severe infections should be treated with oral itraconazole for a period of 12 weeks

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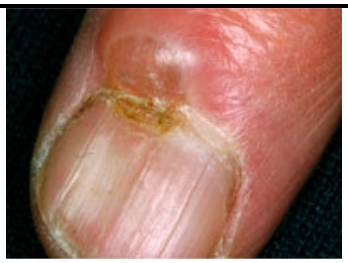
Myxoid cysts (also known as mucous cysts) are benign ganglion cysts usually found on the distal, dorsal aspect of the finger. There is usually osteoarthritis in the surrounding joint. They are more common in middle-aged women

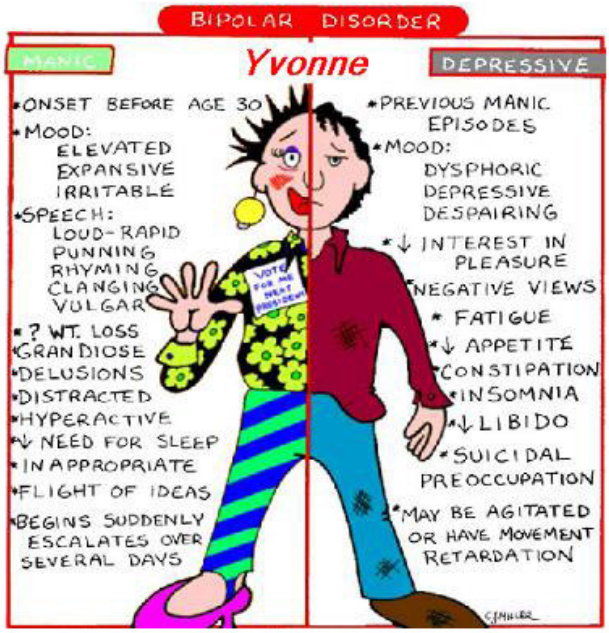


Onycholysis describes the separation of the nail plate from the nail bed

Causes

- Idiopathic
- Trauma e.g. Excessive manicuring
- Infection: especially fungal
- Skin disease: psoriasis, dermatitis
- Impaired peripheral circulation e.g. Raynaud's
- Systemic disease: hyper- and hypothyroidism

PSYCHIATRY


BIPOLAR DISORDER
MANIC
Yvonne
DEPRESSIVE
*ONSET BEFORE AGE 30
*MOOD:
ELEVATED
EXPANSIVE
IRRITABLE
*SPEECH:
LOUD-RAPID
PUNNING
RHYMING
CLANGING
VULGAR
*? WT. LOSS
*GRANDIOSE
*DELUSIONS
*DISTRACTED
*HYPERACTIVE
*↓ NEED FOR SLEEP
*INAPPROPRIATE
*FLIGHT OF IDEAS
*BEGINS SUDDENLY
ESCALATES OVER
SEVERAL DAYS
*PREVIOUS MANIC
EPISODES
*MOOD:
DYSPHORIC
DEPRESSIVE
DESPAIRING
*↓ INTEREST IN
PLEASURE
*NEGATIVE VIEWS
* FATIGUE
*↓ APPETITE
*CONSTIPATION
*INSOMNIA
*↓ LIBIDO
*SUICIDAL
PREOCCUPATION
*MAY BE AGITATED
OR HAVE MOVEMENT
RETARDATION

Symptoms without organic disease: there are a wide variety of psychiatric terms for patients who have symptoms for which no organic cause can be found:

Unexplained symptoms
- **S**omatisation = **S**ymptoms
- Hypo**C**hondria = **C**ancer

Somatisation disorder
- Multiple physical SYMPTOMS present for at least 2 years
- Patient refuses to accept reassurance or negative test results

Hypochondrial disorder
- Persistent belief in the presence of an underlying serious DISEASE, e.g. Cancer
- Patient again refuses to accept reassurance or negative test results

Conversion disorder
- Typically involve loss of motor or sensory function
- Some patients may experience secondary gain from loss of function
- Patients may be indifferent to their apparent disorder
- Psychogenic aphonia is a form of conversion disorder: not speaking after a shocking event.

Dissociative disorder
- Dissociation is a process of 'separating off' certain memories from normal consciousness
- In contrast to conversion disorder involves psychiatric symptoms e.g. Amnesia, fugue, stupor
- Dissociative identity disorder (DID) is the new term for multiple personality disorder as is the most severe form of dissociative disorder

Munchausen's syndrome
- Also known as factitious disorder
- The intentional production of physical or psychological symptoms

Malingering
- Fraudulent simulation or exaggeration of symptoms with the intention of financial or other gain

Body dysmorphic disorder (sometimes referred to as dysmorphophobia) is a mental disorder where patients have a significantly distorted body image

Diagnostic and Statistical Manual (DSM) IV criteria:
- Preoccupation with an imagine defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive
- The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- The preoccupation is not better accounted for by another mental disorder (e.g., dissatisfaction with body shape and size in Anorexia Nervosa)

Seasonal affective disorder (SAD) describes depression which occurs predominately around the winter months. Bright light therapy has been shown to be more effective than placebo for patients with SAD

Post-traumatic stress disorder (PTSD) can develop in people of any age following a traumatic event, for example a major disaster or childhood sexual abuse. It encompasses what became known as 'shell shock' following the First World War. One of the DSM-IV diagnostic criteria is that symptoms have been present for more than one month

Features

- Re-experiencing: flashbacks, nightmares, repetitive and distressing intrusive images
- Avoidance: avoiding people, situations or circumstances resembling or associated with the event
- Hyperarousal: hypervigilance for threat, exaggerated startle response, sleep problems, irritability and difficulty concentrating
- Emotional numbing - lack of ability to experience feelings, feeling detached from other people
- Depression
- Drug or alcohol misuse
- Anger
- Unexplained physical symptoms

Management

- Following a traumatic event single-session interventions (often referred to as debriefing) are not recommended
- Watchful waiting may be used for mild symptoms lasting less than 4 weeks
- Trauma-focused cognitive behavioural therapy (CBT) or eye movement desensitisation and reprocessing (EMDR) therapy may be used in more severe cases
- Drug treatments for PTSD should not be used as a routine first-line treatment for adults. If drug treatment is used then paroxetine or mirtazapine are recommended

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Post-concussion syndrome is seen after even minor head trauma

Typical features include

- Headache
- Fatigue
- Anxiety/depression
- Dizziness

Mania & Hypomania: presence of psychotic symptoms differentiates mania from hypomania

Psychotic symptoms

- Delusions of grandeur
- Auditory hallucinations

The following symptoms are common to both hypomania and mania

Mood	Speech and thought	Behaviour
• Predominately elevated • Irritable	• Pressured • Flight of ideas • Poor attention	• Insomnia • Loss of inhibitions: sexual promiscuity, overspending, risk-taking • ↑ appetite

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Sleep paralysis is a common condition characterized by transient paralysis of skeletal muscles which occurs when awakening from sleep or less often while falling asleep. It is thought to be related to the paralysis that occurs as a natural part of REM (rapid eye movement) sleep. Sleep paralysis is recognised in a wide variety of cultures

Features

- Paralysis - this occurs after waking up or shortly before falling asleep
- Hallucinations - images or speaking that appear during the paralysis

Management

- if troublesome clonazepam may be used

Post-partum mental health problems range from the 'baby-blues' to puerperal psychosis

'Baby-blues'	Postnatal depression	Puerperal psychosis
Seen in around 60-70% of women Typically 3-7 days following birth and more common in primips Mothers: characteristically anxious, tearful and irritable	Affects around 10% of women Most cases start within a month and typically peaks at 3 months Features are similar to depression seen in other circumstances	Affects approximately 0.2% of women Onset usually within the first 2-3 weeks following birth Features include severe swings in mood (similar to bipolar disorder) and disordered perception (e.g. auditory hallucinations)
Reassurance and support, the health visitor has a key role	As with the baby blues reassurance and support are important Cognitive behavioural therapy may be beneficial. Certain SSRIs such as sertraline may be used if symptoms are severe* - whilst they are secreted in breast milk it is not thought to be harmful to the infant	Admission to hospital is usually required There is around a 20% risk of recurrence following future pregnancies

*fluoxetine is best avoided due to a long half-life

Obsessive compulsive disorder (OCD)

Pathophysiology

- some research suggest childhood group A β-hemolytic streptococcal infection may have a role

Associations

- Depression (30%)
- Schizophrenia (3%)
- Sydenham's chorea
- Tourette's syndrome
- Anorexia nervosa

Schizophrenia: Schneider's first rank symptoms may be divided into auditory hallucinations, thought disorders, passivity phenomena and delusional perceptions:

Auditory hallucinations of a specific type:
- Two or more voices discussing the patient in the third person
- Thought echo
- Voices commenting on the patient's behaviour

Thought disorder (occasionally referred to as thought alienation):
- Thought insertion
- Thought withdrawal
- Thought broadcasting

Passivity phenomena:
- Bodily sensations being controlled by external influence
- Actions/impulses/feelings - experiences which are imposed on the individual or influenced by others

Delusional perceptions
- A two stage process: where first a normal object is perceived then secondly there is a sudden intense delusional insight into the objects meaning for the patient e.g. 'the traffic light is green therefore i am the king'.

Other features of schizophrenia include
- Impaired insight
- Incongruity/blunting of affect (inappropriate emotion for circumstances)
- ↓ speech
- Neologisms: made-up words
- Catatonia
- Negative symptoms: incongruity/blunting of affect, anhedonia (inability to derive pleasure), alogia (poverty of speech), avolition (poor motivation)

Factors associated with poor prognosis
- Strong family history
- Gradual onset
- Low IQ
- Premorbid history of social withdrawal
- Lack of obvious precipitant

Risk of developing schizophrenia
- Monozygotic twin has schizophrenia = 50%
- Parent has schizophrenia = 10-15%
- Sibling has schizophrenia = 10%
- No relatives with schizophrenia = 1%

Concrete thinking:
When a patient cannot use abstraction to understand the meaning of a sentence. It is more common in schizophrenia. Literal thinking is of course a feature of autism.

Alcohol withdrawal

Alcohol withdrawal
- Symptoms: 6-12 hours
- Seizures: 36 hours
- Delirium tremens: 72 hours

Mechanism
- Chronic alcohol consumption enhances GABA mediated inhibition in the CNS (similar to benzodiazepines) and inhibits NMDA-type glutamate receptors
- Alcohol withdrawal is thought to lead to the opposite (↓ inhibitory GABA and ↑ NMDA glutamate transmission)

Features
- Symptoms start at 6-12 hours
- Peak incidence of seizures at 36 hours
- Peak incidence of delirium tremens is at 72 hours

Management
- Benzodiazepines
- Carbamazepine also effective in treatment of alcohol withdrawal
- Phenytoin is said not to be as effective in the treatment of alcohol withdrawal seizures

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Bulimia nervosa is a type of eating disorder characterized by episodes of binge eating followed by intentional vomiting

Management
- Referral for specialist care is appropriate in all cases
- Cognitive behaviour therapy (CBT) is currently consider first-line treatment
- Interpersonal psychotherapy is also used but takes much longer than CBT
- Pharmacological treatments have a limited role - a trial of high-dose fluoxetine is currently licensed for bulimia but long-term data is lacking

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Anorexia Nervosa Features of include:
- A phobic avoidance of normal weight
- Relentless dieting
- Self-induced vomiting
- Laxative abuse
- Excessive exercise
- Amenorrhoea
- Lanugo hair
- Hypotension
- Denial
- Concealment
- Overperception of body image
- Enmeshed families.
- Impaired glucose tolerance

Anorexia features

- Most things low
- **G**'s and **C**'s raised: **g**rowth hormone, **g**lucose, salivary **g**lands, **c**ortisol, **c**holesterol, **c**arotinemia

Anorexia nervosa is associated with a number of characteristic clinical signs and physiological abnormalities which are summarised below

Features

- Loss of axillary and pubic hair
- Bradycardia
- Hypotension
- Enlarged salivary glands

Physiological abnormalities

- Hypokalemia
- Low FSH, LH, estrogens and testosterone
- Raised cortisol and growth hormone
- Impaired glucose tolerance
- Hypercholesterolemia
- Hypercarotinemia
- Low T3

Hospitalized patients with AN and NGT feeding are at risk of refeeding syndrome, which can lead to profound hypophosphatemia

Anorexia nervosa is the most common cause of admissions to child and adolescent psychiatric wards.

Epidemiology

- 90% of patients are ♀
- Predominately affects teenage and young-adult ♀s
- Prevalence of between 0.5-1%

Diagnosis (based on the DSM-IV criteria)

- Person chooses not to eat - BMI < 17.5 kg/m^2, or < 85% of that expected
- Intense fear of being obese
- Disturbance of weight perception
- Amenorrhoea = 3 consecutive cycles

The prognosis of anorexia nervosa remains poor. 10% of patients will eventually die.

Suicide: factors associated with risk of suicide following an episode of deliberate self harm:

- Efforts to avoid discovery
- Planning
- Leaving a written note
- Final acts such as sorting out finances
- Violent method

These are in addition to standard risk factors for suicide:

- ♂ sex
- ↑ age
- Unemployment or social isolation
- Divorced or widowed
- History of mental illness (depression, schizophrenia)
- History of deliberate self harm
- Alcohol or drug misuse

Employment is a protective factor

Chronic Fatigue Syndrome: diagnosed after at least 4 months of disabling fatigue affecting mental and physical function more than 50% of the time in the absence of other disease which may explain symptoms

Epidemiology

- More common in ♀s
- Past psychiatric history has not been shown to be a risk factor

Fatigue is the central feature, **other recognised features** include:

- Sleep problems, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep–wake cycle
- Muscle and/or joint pains
- Headaches
- Painful lymph nodes without enlargement
- Sore throat
- Cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding
- Physical or mental exertion makes symptoms worse
- General malaise or 'flu-like' symptoms
- Dizziness
- Nausea
- Palpitations

Investigation

- NICE guidelines suggest carrying out a large number of screening blood tests to exclude other pathology e.g. FBC, U&E, LFT, glucose, TFT, ESR, CRP, calcium, CK, ferritin*, coeliac screening and also urinalysis

Management

- CBT - very effective, number needed to treat = 2
- Graded exercise therapy - a formal supervised program, do not advise to go to the gym
- 'Pacing' - organising activities to avoid tiring
- Low-dose amitriptyline may be useful for poor sleep
- Referral to a pain management clinic if pain is a predominant feature

Better prognosis in children

Serotonin Syndrome: is a potentially life-threatening adverse drug reaction that may occur following therapeutic drug use, inadvertent interactions between drugs, overdose of particular drugs, or the recreational use of certain drugs. Serotonin syndrome is not an idiosyncratic drug reaction; it is a predictable consequence of excess serotonergic activity at CNS and peripheral serotonin receptors. For this reason, some experts strongly prefer the terms serotonin toxicity or serotonin toxidrome because it is a form of poisoning. It may also be called serotonin sickness, serotonin storm, serotonin poisoning, hyperserotonemia, or serotonergic syndrome.

Features	Causes (drugs that lead to ↑ serotonin):	Management
• Agitation • Hyperthermia • Tachycardia • Labile BP • Hyperreflexia and ↑ tone	• SSRI • MAOI (e.g. Moclobemide)	• Remove the causative factor • Supportive measures

Restless legs syndrome (RLS) is a syndrome of spontaneous, continuous lower limb movements that may be associated with paraesthesia. It is extremely common, affecting between 2-10% of the general population. Males and females are equally affected and a family history may be present

Clinical features

- Uncontrollable urge to move legs (akathisia). Symptoms initially occur at night but as condition progresses may occur during the day. Symptoms are worse at rest
- Paraesthesias e.g. 'Crawling' or 'throbbing' sensations
- Movements during sleep may be noted by the partner - periodic limb movements of sleeps (PLMS)

Causes and associations

- There is a positive family history in 50% of patients with idiopathic RLS
- **Iron deficiency anaemia**
- **Uraemia**
- Diabetes mellitus
- Pregnancy

The diagnosis is clinical although bloods to exclude iron deficiency anaemia may be appropriate

Management

- Simple measures: walking, stretching, massaging affected limbs
- Treat any iron deficiency
- Dopamine agonists are first-line treatment (e.g. Pramipexole, ropinirole)
- Benzodiazepines
- Gabapentin

Cognitive Behavioural Therapy (CBT):

Main points

- Useful in the management of depression and anxiety disorders
- Usually consists of one to two hour sessions once per week
- Should be completed within 6 months
- Patients usually get around 16-20 hours in total

Antipsychotics: act as dopamine D2 receptor antagonists, blocking dopaminergic transmission in the mesolimbic pathways. Conventional antipsychotics are associated with problematic extrapyramidal side-effects which has led to the development of atypical antipsychotics such as clozapine

Extrapyramidal side-effects

- Parkinsonism
- Acute dystonia (e.g. Torticollis, oculogyric crisis)
- Akathisia (severe restlessness)
- Tardive dyskinesia (late onset of choreoathetoid movements, abnormal, involuntary, may occur in 40% of patients, may be irreversible, most common is chewing and pouting of jaw)

Other side-effects/features

- Antimuscarinic: dry mouth, blurred vision, urinary retention, constipation
- Sedation, weight gain
- Raised prolactin: galactorrhoea
- Neuroleptic malignant syndrome: pyrexia, muscle stiffness
- ↓ seizure threshold (greater with atypicals)
- Antipsychotics are not addictive

Atypical antipsychotics should now be used first-line in patients with schizophrenia, according to 2005 NICE guidelines. The main advantage of the atypical agents is a significant reduction in extra-pyramidal side-effects.

Olanzapine, like other atypical antipsychotics, is known to block serotonin receptors (especially 5-HT2 subtype) as well as D2 dopamine receptors

Adverse effects of atypical antipsychotics

- Weight gain
- ↑ risk of venous thromboembolism
- Olanzapine and risperidone are associated with an ↑ risk of stroke in elderly patients
- Clozapine is associated with agranulocytosis (see below)

Examples of atypical antipsychotics

- Clozapine
- Olanzapine
- Risperidone (affinity for serotonin 5-HT2A receptor > D2 receptors)
- Quetiapine
- Amisulpride

Clozapine, one of the first atypical agents to be developed, carries a significant risk of agranulocytosis and full blood count monitoring is therefore essential during treatment. For this reason clozapine should only be used in patients resistant to other antipsychotic medication

Adverse effects of clozapine

- Agranulocytosis (1%), neutropaenia (3%)
- ↓ seizure threshold - can induce seizures in up to 3% of patients

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Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for the majority of patients with depression:

- Citalopram and fluoxetine are currently the preferred ssris
- Citalopram is useful for elderly patients as it is associated with lower risks of drug interactions
- Sertraline is useful post myocardial infarction as there is more evidence for its safe use in this situation than other antidepressants
- SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated

Adverse effects

- Gastrointestinal symptoms are the most common side-effect
- There is an increased risk of gastrointestinal bleeding in patients taking SSRIs. A proton pump inhibitor should be prescribed if a patient is also taking a NSAID
- Patients should be counselled to be vigilant for increased anxiety and agitation after starting a SSRI
- Fluoxetine and paroxetine have a higher propensity for drug interactions
- Citalopram and sertraline and more suitable for patients with chronic physical health problems as they have a lower propensity for drug interactions.

Interactions

- NSAIDs: NICE advised 'do not normally offer SSRIs', but if given co-prescribe a proton pump inhibitor
- Warfarin / heparin: NICE guidelines recommend avoiding SSRIs and considering mirtazapine
- Aspirin: see above
- Triptans: avoid SSRIs

Following the initiation of antidepressant therapy patients should normally be reviewed by a doctor after 2 weeks. For patients under the age of 30 years or at increased risk of suicide they should be reviewed after 1 week. If a patient makes a good response to antidepressant therapy they should continue on treatment for at least 6 months after remission as this reduces the risk of relapse.

When stopping a SSRI the dose should be gradually reduced over a 4 week period (this is not necessary with fluoxetine). Paroxetine has a higher incidence of discontinuation symptoms.

Discontinuation symptoms

- Increased mood change
- Restlessness
- Difficulty sleeping
- Unsteadiness
- Sweating
- Gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting
- Paraesthesia

Tricyclic antidepressants (TCAs) are used less commonly now for depression due to their side-effects and toxicity in overdose. They are however used widely in the treatment of neuropathic pain, where smaller doses are typically required.

Common side-effects:

- Drowsiness
- Dry mouth
- Constipation
- Urinary retention
- Blurred vision

Choice of tricyclic

- Low-dose amitriptyline is commonly used in the management of neuropathic pain and the prophylaxis of headache (both tension and migraine)
- Lofepramine has a lower incidence of toxicity in overdose
- Amitriptyline and dosulepin (dothiepin) and considered the most dangerous in overdose

More sedative	Less sedative
Amitriptyline	Imipramine
Clomipramine	Lofepramine
Dosulepin	Nortriptyline
Trazodone	

Neuroleptic Malignant Syndrome is a rare but dangerous condition seen in patients taking antipsychotic medication. It carries a mortality of up to 10% and can also occur with atypical antipsychotics

Features

- More common in young ♂ patients
- Onset usually in first 10 days of treatment or after increasing dose
- Pyrexia
- Rigidity
- Tachycardia

A raised creatine kinase is present in most cases. A leukocytosis may also be seen

Management

- Stop antipsychotic
- IV fluids to prevent renal failure
- Dantrolene may be useful in selected cases
- Bromocriptine, dopamine agonist, may also be used

Electroconvulsive therapy is a useful treatment option for patients with severe depression refractory to medication or those with psychotic symptoms. The only absolute contraindication is raised intracranial pressure.

Short-term side-effects:

- Headache
- Short term memory impairment
- Memory loss of events prior to ECT
- Cardiac arrhythmia
- Physical complications: fractures, dislocations etc

Long-term side-effects: Some patients report impaired memory

Professor Tijani Elmahi (1911-1970)
Father of Psychiatry in Sudan and Africa

ولد التيجاني الماحي في بلدة الكوة على ضفاف النيل الأبيض جنوب الخرطوم في ٧ إبريل ١٩١١. تلقى تعليمه الأولي في الكوة والأوسط في رفاعة والثانوي في الخرطوم، ثم تخرج في مدرسة كتشنر الطبية في عام ١٩٣٥ حائزاً على دبلوم الباطنية والجراحة والتوليد عمل بعدها طبيباً بالمصلحة الطبية (وزارة الصحة لاحقاً) في أم درمان، الخرطوم، وادي حلفا وكوستي. التحق التيجاني بمعهد الطب العقلي والنفسي بجامعة لندن في عام ١٩٤٧ حيث تخصص في الطب النفسي بنيله دبلوم الطب النفسي في يوليو 1949، فكان بذلك أول طبيب سوداني وأول إفريقي يجاز في هذا العلم، ولذلك لقب بأبي الطب النفسي في إفريقيا. بعد أن عاد من إنجلترا وتسلم عمله كأخصائي في الأمراض النفسية، قام بتأسيس أول عيادة للطب النفسي والأمراض العصبية بالمصلحة الطبية السودانية في السودان بالخرطوم بحري في أكتوبر ١٩٥٠.

في عام ١٩٥٦ تطوع في الخدمة العسكرية دفاعاً عن مصر إبان العدوان الثلاثي .ومن عام ١٩٥٩ إلى ١٩٦٤ شغل منصب مستشار الصحة العقلية لمنطقة شرق حوض البحر المتوسط (منظمة الصحة العالمية) بالإسكندرية، وكان عضواً في لجنة الصحة العقلية وعضواً في اللجنة التنفيذية للإتحاد العالمي للصحة العقلية.

بعد ثورة ٢١ أكتوبر ١٩٦٤، اختير التيجاني الماحي عضواً ورئيساً مناوباً لمجلس السيادة السوداني. وفي ١٩٦٩ عرضت عليه جامعة الخرطوم كرسي الأستاذية في الطب النفسي فقبله والتحق بالجامعة رسمياً، وانصرف لتأسيس قسم الأمراض العصبية والنفسية بكلية الطب حيث كان يعمل إلى أن وافته المنية في الساعات الأولى من صباح الخميس ٨ يناير ١٩٧٠. تزوج التيجاني الماحي في عام ١٩٣٧ وأنجب أربعة أولاد وبنتين.

أثناء حياته، انتخب التيجاني الماحي نقيباً لأطباء السودان ورئيساً للجمعية الطبية السودانية وعضواً في مجمع اللغة العربية بالقاهرة، ومنح درجة الدكتوراه في العلوم من كل من جامعة كولومبيا بالولايات المتحدة وجامعة الخرطوم تكريماً له. وبعد وفاته، سميت مستشفى التيجاني الماحي بأم درمان وقاعة محاضرات بكلية الطب، جامعة الخرطوم باسمه .

التيجاني الماحي مثقف موسوعي المعرفة جعل من تخصصه في علم النفس نقطة انطلاق للإنفتاح على جميع المعارف الإنسانية، وقد أجاد اللغة الإنجليزية إلى جانب العربية وألم ببعض اللغات القديمة مثل الهيروغليفية . استطاع التيجاني توظيف مؤهلاته المتعددة والمتنوعة وخبرته في الطب النفسي في إعداد مساهمات فكرية عرفت بالدقة والعمق، فكتب في علم الإدارة وفي التاريخ واللغات والآداب إلى جانب كتاباته في مجال تخصصه في علم النفس والصحة العقلية. وتتجلى إمكانات التيجاني الماحي الموسوعية في واحدة من أهم مساهماته ألا وهي مؤلفه

مقدمة في تاريخ الطب العربي الذي رمى من ورائه إلى إثبات الرصيد الثر الذي يملكه العرب في مجال الطب . والكتاب موسوعة صغيرة تؤرخ للطب العربي استخدم فيه التيجاني جماع خبرته ومعرفته في الطب وحشد له عشرات المراجع باللغتين العربية والإنجليزية، وختمه بفهرس شامل لأعلام الأطباء القدماء، وفهرس آخر للأمراض. إضافة لهذا السفر القيم، كتب التيجاني الماحي العشرات من الدراسات والأبحاث العلمية وجميعها تعبر عن عمق ثقافته وعلمه. جمع دكتور أحمد الصافي أعمال التيجاني الماحي المشتتة وحققها مع الدكتور طه بعشر ونشر الأعمال الإنجليزية في ١٩٨١ والعربية.
في ١٩٨٤ في دار النشر جامعة الخرطوم. أما مقالات التيجاني عن الزار التي نشرها في ١٩٤٦ ومخطوطاته التي وصف فيها مشايخ الزار في السودان في الفترة من ١٩٣٥ إلى ١٩٦٧ فستظهر قريباً.

كان التيجاني يؤمن بالتبادل الحضاري والاستفادة من الخبرة الإنسانية وكان فكره واسعاً بالقدر الذي يجعله بعيداً عن كل تعصب وأكبر من كل قالب ومع ذلك ففي تقديره لوسائل الإصلاح ولأساليب الثورة كان الدكتور التيجاني لا يرفع عينيه عن مواطئ أقدامه إذ كان يحس بأن الخامات المحلية والأفكار الملتصقة بالأرض هي التي يمكن أن تخلق الظروف المواتية للتغيير الاجتماعي.

اهتم التيجاني الماحي بالترجمة من العربية إلى الإنجليزية إلى غيرها من اللغات التي أجادها وقام بترجمة بعض القصائد العربية منها قصائد للشاعر الكبير نزار قباني. وقد وفق التيجاني الماحي في ترجمته وحافظ على شاعرية نزار المتدفقة. أهم تلك الأعمال كانت ترجمته لقصائد (أنت لي) و(قصائد) و(خبز وحشيش وقمر) التي كتب مقدمتها الأستاذ جمال محمد أحمد.

امتلك التيجاني الماحي مكتبة شخصية حوت نفائس الكتب والمصنفات، أهدتها أسرته إلى جامعة الخرطوم وآلت إليها في ١٩٧٢ حيث أسس قسم في مكتبتها باسمه. حوت (مكتبة التيجاني الماحي) حوالي ٢٠٠٠٠ كتاب في تاريخ العلم والفلسفة والدين والرياضيات والفيزياء والكيمياء وعلم الفلك والزراعة والجغرافيا وعلم النبات والحيوان والتربية والعلوم الاجتماعية والسياسية والاقتصادية والفنون التطبيقية والموسيقى والآداب وأدب الرحلات والموسوعات والقواميس .حوت تلك المكتبة ١٥٠٠ كتاب عن السودان و١٠٠٠ في الطب منها ٢٧٠ كتاباً باللغة العربية، ٧٦٠ خريطة نادرة و٣٥٠٠ مخطوطة أصلية زيادة على طوابع وأفلام سينمائية نادرة. نوهنا مراراً إلى أن تلك المكتبة تحوي مخطوطات عربية وإسلامية وسودانية نادرة، وأشرنا إلى أن تلك الإضافة جعلت مكتبة جامعة الخرطوم غنية بالمخطوطات النادرة، وأعربنا عن أملنا في أن يتجه الاهتمام القومي إلى حصر ووصف وتصنيف وفهرسة هذه المغتنيات وتصويرها وخزنها وحفظها من التلف، ثم إتاحتها للقراء والباحثين.

Wisdom from the Father of African Psychiatry

By Gerald D. Klee, MD

The audience was captivated by Tigani El Mahi, MD when he addressed a scientific meeting of the MPS in 1958.
Dr. El Mahi, a citizen of the Sudan, represented the World Health Association (WHO) for North Africa. His talk was on psychiatry in Africa, a subject about which we knew very little.
A native of Sudan, Dr. El Mahi was a deeply learned man and a profound scholar in the Islamic faith. His extensive psychiatric training took place in major European centers followed by a stint at Johns Hopkins under Adolf Meyer. After completing his training he returned to Khartoum, Sudan and hung out his shingle.
Psychiatric disorders tend to be fundamentally similar in all parts of the world, but their expression can vary widely due to cultural differences. El Mahi was disappointed to find that despite his use of the best methods known to Western science many of his African patients didn't do so well. He wondered why.

He discovered that patients from traditional African communities were far more satisfied under the care of traditional healers. In the best scientific tradition, he made extensive observations of the methods used by traditional healers to see what accounted for their success.

He found that traditional healers were also practitioners of indigenous African religions. Their methods included exorcising evil spirits and combating spells cast by witches. The patient's ancestors were called upon to exert spiritual influence. These treatments were performed in the village with the patient's family participating. There was dancing, singing and prayers to ancestors. Sometimes the whole village participated. Even among patients who had converted to Christianity or to Islam, traditional religious practices were usually employed.

"How can these superstitious approaches be more successful than the scientific methods of Europe and the US?" Dr. El Mahi wondered.

As he continued his observations, El Mahi developed increasing respect for native healers. It dawned on him that his prized Western methods were utterly foreign to African patients from traditional cultures. He realized that could account for his ineffectiveness. In contrast to his western, "scientific" approach, the methods of traditional healers were deeply meaningful to such patients and their families and consequently yielded greater satisfaction.
In a simple sentence, El Mahi explained why the traditional healers got better results than he did. "When the patient and the doctor agree, the patient gets well", he said. That sounded like good common sense. He then added that he heard it years ago from Adolf Meyer at Johns Hopkins.
But what does it mean? El Mahi explained that the patient needs to feel that the doctor/healer understands him. If the patient believes that the root of his illness is due to witchcraft or evil spirits, it doesn't help to tell him he's wrong.

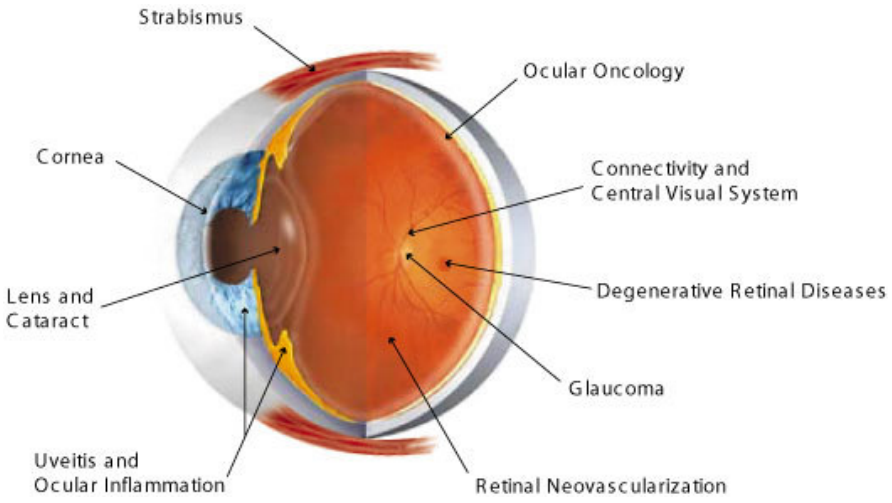
A great deal of mutual respect developed between El Mahi and traditional healers as they worked together in treating the same patients. The results were good. Instead of seeing conflict between theories and disciplines, they saw good therapeutic outcomes.

As Dr. El Mahi's approach to understanding and treating mental patients became widespread in Africa he became known as the father of African psychiatry.

Even today, most of Africa suffers severe shortages of doctors and other trained health care workers. Traditional healers help to fill the gaps.

Strange as it may seem to Americans, the Tigani El Mahi story has relevance in the US and elsewhere. Americans also have various belief systems and folkways that influence their ideas about illness and health. Our most advanced scientific methods will be less effective if we ignore Doctor Tigani El Mahi's African wisdom. American psychiatrists don't need to team up with traditional healers, but we must take the time and effort to learn what is important to patients and to take it into consideration.

OPHTHALMOLOGY



Please note that boxes colored with this color are for Part II – that includes Fundoscopic findings

Macular degeneration is the most common cause of blindness in the UK. Degeneration of the central retina (macula) is the key feature with changes usually bilateral.

Traditionally two forms of macular degeneration are seen:

- **D**ry macular degeneration: characterized by **D**rusen - yellow round spots in Bruch's membrane
- Wet (exudative, neovascular) macular degeneration: characterized by choroidal neovascularisation. Leakage of serous fluid and blood can subsequently result in a rapid loss of vision. Carries worst prognosis

Recently there has been a move to a more updated classification (based on Fluorescein angiography):

- Early age related macular degeneration (non-exudative, age related maculopathy): drusen and alterations to the retinal pigment epithelium (RPE)
- Late age related macular degeneration (neovascularisation, exudative)

Risk factors

- Age: most patients are over 60 years of age
- Family history
- Smoking
- More common in caucasians
- ♀ sex
- High cumulative sunlight exposure

Normal Vision

Features

- ↓ visual acuity: 'blurred', 'distorted' vision, central vision is affected first
- Central scotomas
- Fundoscopy: drusen, pigmentary changes

Same view with age related Macular Degeneration

General management

- Stopping smoking
- High does of β-carotene, vitamins C and E, and zinc may help to slow down visual loss for patients with established macular degeneration. Should avoid smoking due to an ↑ risk of lung cancer

Dry macular degeneration - no current medical treatments

Wet macular degeneration

- Photocoagulation
- Photodynamic therapy
- anti-vascular endothelial growth factor (anti-VEGF) treatments: intravitreal ranibizumab

Sudden Painless Loss of Vision:

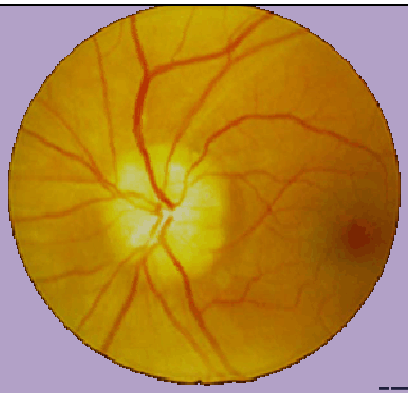
The **most common causes** of a sudden painless loss of vision are as follows:

- Ischemic optic neuropathy (e.g. Temporal arteritis or atherosclerosis)
- Occlusion of central retinal vein
- Occlusion of central retinal artery
- Vitreous hemorrhage
- Retinal detachment

Amaurosis fugax: classically described as a transient monocular vision loss that appears as a "curtain coming down vertically into the field of vision in one eye". Sometimes it occurs as episodes, caused by epsilateral carotid artery diease.

Ischemic optic neuropathy

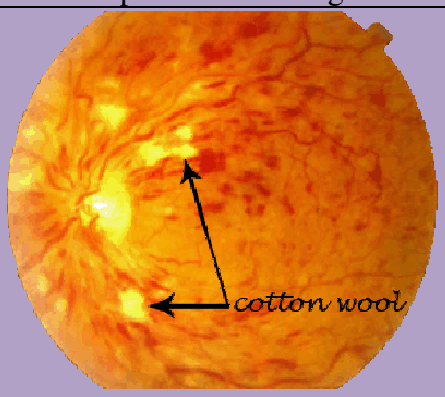
- May be due to arteritis (e.g. Temporal arteritis) or atherosclerosis (e.g. HTN, DM, old patient)
- Due to occlusion of the short posterior ciliary arteries, causing damage to the optic nerve
- Altitudinal field defects are seen → loss of vision above or below the horizontal level



Pale optic disc
Optic disc swelling

Central retinal vein occlusion

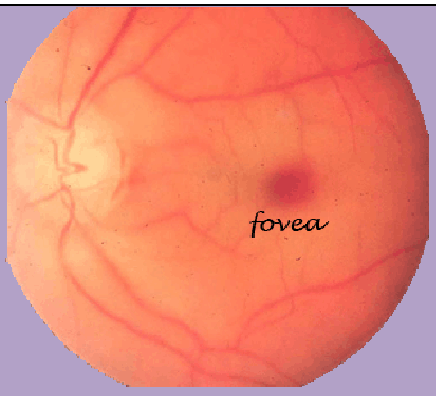
- Incidence ↑ with age, more common than arterial occlusion
- Causes: glaucoma, polycythemia, hypertension



- Widespread retinal hemorrhages in all 4 quadrants, which vary in appearance from a small-scattered retinal hemorrhages to marked confluent hemorrhages
- Marked dilated and tortuous retinal vessels
- Cotton-wool spots
- Optic disc edema, macular edema, and retinal thickening
- Vitreous hemorrhages may be present

Central retinal Artery occlusion

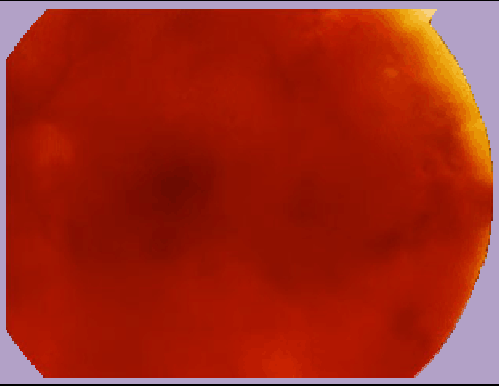
- Due to thromboembolism (from atherosclerosis) or arteritis (e.g. Temporal arteritis)
- Features include Afferent pupillary defect, 'cherry red' spot on a pale retina



Diffuse edema makes the retina and arteries look pale. Perfused underlying tissues show through the thin fovea giving a classic cherry-red spot appearance.

Vitreous hemorrhage

- Causes: diabetes, bleeding disorders
- Features may include sudden visual loss, dark spots



Flashes and floaters are symptoms of vitreous detachment. If present in long standing diabetic, patient is at risk of retinal detachment and should be referred urgently to an ophthalmologist

Retinal detachment

- Features of vitreous detachment, which may precede retinal detachment, include flashes of light or floaters (see below)

Differentiating posterior vitreous detachment, retinal detachment and vitreous hemorrhage

Posterior vitreous detachment	Retinal detachment	Vitreous hemorrhage
• Flashes of light (photopsia) - in the peripheral field of vision • Floaters, often on the temporal side of the central vision	• Dense shadow that starts peripherally progresses towards the central vision • A veil or curtain over the field of vision • Straight lines appear curved (positive Amsler grid test) • Central visual loss	• Large bleeds cause sudden visual loss • Moderate bleeds may be described as numerous dark spots • Small bleeds may cause floaters

Relative afferent pupillary defect: Also known as the Marcus-Gunn pupil, a relative afferent pupillary defect is found by the 'swinging light test'. It is caused by a lesion anterior to the optic chiasm i.e. optic nerve or retina

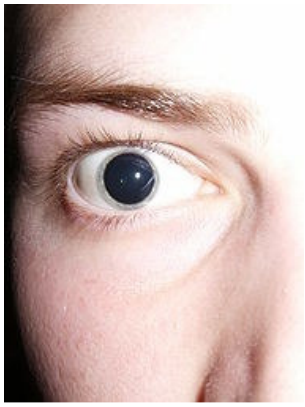
Causes

- Retina: detachment
- Optic nerve: optic neuritis e.g. Multiple sclerosis

Pathway of pupillary light reflex

- Afferent: retina → optic nerve → lateral geniculate body → midbrain
- Efferent: edinger-westphal nucleus (midbrain) → oculomotor nerve

Causes of Mydriasis (large pupil)



- Third nerve palsy
- Holmes-adie pupil
- Traumatic iridoplegia
- Pheochromocytoma
- Congenital

Drug causes of mydriasis

- Topical mydriatics: tropicamide, atropine
- Sympathomimetic drugs: amphetamines
- Anticholinergic drugs: tricyclic antidepressants

Holmes-ADIe pupil is a benign condition most commonly seen in women. It is one of the differentials of a **DI**lated pupil

Overview

- Unilateral in 80% of cases
- Dilated pupil
- Once the pupil has constricted it remains small for an abnormally long time
- Slowly reactive to accommodation but very poorly (if at all) to light

Holmes-Adie syndrome

- Association of Holmes-Adie pupil with absent ankle/knee reflexes

Angioid retinal streaks are seen on fundoscopy as irregular dark red streaks radiating from the optic nerve head. The elastic layer of Bruch's membrane is characteristically thickened and calcified

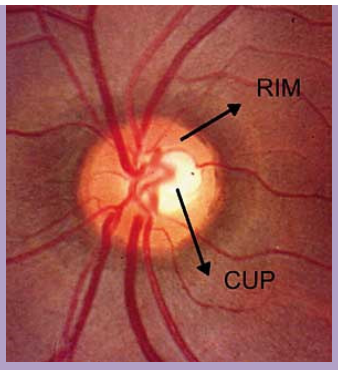
Causes

- Pseudoxanthoma elasticum
- Ehler-danlos syndrome
- Paget's disease
- Sickle-cell anemia
- Acromegaly

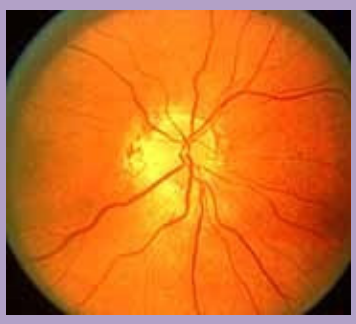
Optic atrophy is seen as pale, well demarcated disc on fundoscopy. It is usually bilateral and causes a gradual loss of vision*. Causes may be acquired or congenital

Acquired causes

- Multiple sclerosis
- papilledema (longstanding)
- raised intraocular pressure (e.g. glaucoma, tumour)
- retinal damage (e.g. choroiditis, retinitis pigmentosa)
- ischemia
- toxins: tobacco amblyopia, quinine, methanol, arsenic, lead
- nutritional: vitamin B1, B2, B6 and B12 deficiency



Normal Optic Disc



Optic Atrophy

Congenital causes

- Friedreich's ataxia
- Mitochondrial disorders e.g. Leber's optic atrophy
- DIDMOAD - the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)

*strictly speaking optic atrophy is a descriptive term, it is the optic neuropathy that results in visual loss

Cataract:

Majority

- Age related
- UV light

Systemic

- DM
- Steroids
- Infection (congenital rubella)
- Metabolic (hypocalcemia, galactosemia)
- Myotonic dystrophy, Down's syndrome

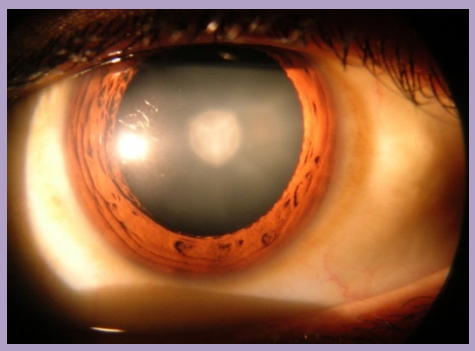
Ocular

- Trauma
- Uveitis
- High myopia
- Topical steroids

A cataract is an opacity of the normally clear lens which may develop as a result of aging, metabolic disorders, trauma or heredity

Classification

- Nuclear: change lens refractive index, common in old age
- Polar: localized, commonly inherited, lie in the visual axis
- Subcapsular: due to steroid use, just deep to the lens capsule, in the visual axis
- Dot opacities: common in normal lenses, also seen in diabetes and myotonic dystrophy



Retinitis pigmentosa primarily affects the peripheral retina resulting in tunnel vision

Features

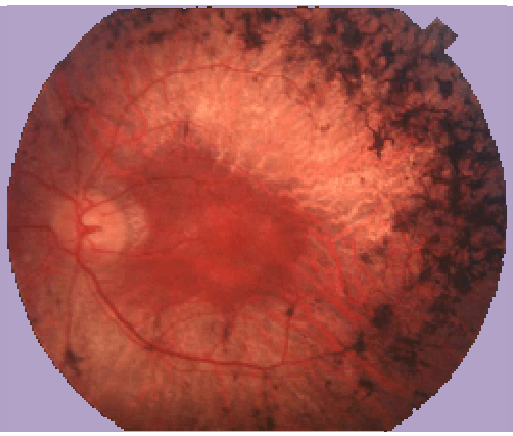
- Night blindness is often the initial sign
- Funnel vision (the preferred term for tunnel vision)

Associated diseases

- Refsum disease: cerebellar ataxia, peripheral neuropathy, deafness, ichthyosis
- Usher syndrome
- Abetalipoproteinemia
- Lawrence-Moon-Biedl syndrome
- Kearns-Sayre syndrome
- Alport's syndrome

Tunnel vision

Fundoscopic Findings: Mottling of the retinal pigment epithelium with black bone-spicule pigmentation is typically indicative (or pathognomonic) of retinitis pigmentosa. Other ocular features include waxy pallor of the optic nerve head, attenuation (thinning) of the retinal vessels, cellophane maculopathy, cystic macular edema and posterior subcapsular cataract



CMV Retinitis: causes hemorrhage at the edge of the area of retinal necrosis

Tunnel vision is the concentric diminution of the visual fields

Causes:

- Papilledema
- Glaucoma
- Retinitis pigmentosa
- Choroidoretinitis
- Optic atrophy secondary to tabes dorsalis
- Hysteria

Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE):

Typical CHRPE:

- Gray or black depigmented lacunae
- Found in 1 quadrant of eye
- Do not affect vision

Atypical CHRPE:

- White fish tail shaped bilaterally
- Affect the vision when there are > 4 in each eye
- Associated with Adenosis polyposis and Gardner's syndrome → do colonoscopy.

Glaucoma is a group disorders characterized by optic neuropathy due, in the majority of patients, to raised intraocular pressure (IOP). It is now recognised that a minority of patients with raised IOP do not have glaucoma and vice versa

In **acute angle closure glaucoma (AACG)** there is a rise in IOP secondary to an impairment of aqueous outflow. Factors predisposing to AACG include:

- Hypermetropia (long-sightedness)
- Pupillary dilatation
- Lens growth associated with age

Mydriatic drops are a known precipitant of acute angle closure glaucoma. Drugs which may precipitate acute glaucoma include anticholinergics and tricyclic antidepressants.

Features

- Severe pain: may be ocular or headache
- ↓ visual acuity
- Symptoms worse with mydriasis (e.g. Watching TV in a dark room)
- Hard, red eye
- Haloes around lights
- Semi-dilated non-reacting pupil
- Corneal edema results in dull or hazy cornea
- Systemic upset may be seen, such as nausea and vomiting and even abdominal pain

Treatment of acute glaucoma - acetazolamide + pilocarpine

Management

- Urgent referral to an ophthalmologist
- Management options include reducing aqueous secretion with acetazolamide and pupillary constriction with topical pilocarpine

Acute angle closure glaucoma is associated with hypermetropia
Primary open-angle glaucoma is associated with myopia

Primary open-angle glaucoma (POAG) also referred to as chronic simple glaucoma: it is present in around 2% of people older than 40 years. Other than age, **risk factors include**:

- Family history
- Black patients
- Myopia
- Hypertension
- Diabetes mellitus

POAG may present insidiously and for this reason is often detected during routine optometry appointments. **Features may include:**

- Peripheral visual field loss - nasal scotomas progressing to 'tunnel vision'
- ↓ visual acuity
- Optic disc cupping

The majority of patients with primary open-angle glaucoma are managed with eye drops. These aim to lower intra-ocular pressure which in turn has been shown to prevent progressive loss of visual field.

Medication	Mode of action	Notes
Prostaglandin analogues (e.g. Latanoprost)	↑ uveoscleral outflow	Once daily administration Adverse effects include brown pigmentation of the iris
β-blockers (e.g. Timolol)	↓ aqueous production	Should be avoided in asthmatics and patients with heart block
Sympathomimetics (e.g. Brimonidine, an α2-adrenoceptor agonist)	↓ aqueous production and ↑ outflow	Avoid if taking MAOI or tricyclic antidepressants Adverse effects include hyperemia
Carbonic anhydrase inhibitors (e.g. Dorzolamide)	↓ aqueous production	Systemic absorption may cause sulphonamide-like reactions
Miotics (e.g. Pilocarpine)	↑ uveoscleral outflow	Adverse effects included a constricted pupil, headache and blurred vision

Surgery in the form of a trabeculectomy may be considered in refractory cases.

Red Eye: there are many possible causes of a red eye. It is important to be able to recognise the causes which require urgent referral to an ophthalmologist. Below is a brief summary of the key distinguishing features

Red eye - glaucoma or uveitis?

- Glaucoma: severe pain, haloes, 'semi-dilated' pupil
- Uveitis: small, fixed oval pupil, ciliary flush

Causes:

- Acute angle closure glaucoma
- Anterior uveitis
- Scleritis
- Conjunctivitis
- Subconjunctival hemorrhage

Acute angle closure glaucoma

- Severe pain (may be ocular or headache)
- ↓ visual acuity, patient sees haloes
- Semi-dilated pupil
- Hazy cornea

Scleritis

- Severe pain (may be worse on movement) and tenderness
- May be underlying autoimmune disease e.g. Rheumatoid arthritis

Anterior uveitis

- Acute onset
- Pain
- Blurred vision and photophobia
- Small, fixed oval pupil, ciliary flush

Conjunctivitis

- Purulent discharge if bacterial, clear discharge if viral

Subconjunctival hemorrhage

- History of trauma or coughing bouts

Lacrimal Glands problems:

Dacryocystitis is infection of the lacrimal sac, **Features:**

- Watering eye (epiphora)
- Swelling and erythema at the inner canthus of the eye

Management is with **systemic antibiotics**. (IV antibiotics are indicated if there is associated periorbital cellulitis)

Congenital lacrimal duct obstruction affects around 5-10% of newborns. It is bilateral in around 20% of cases. **Features:**

- Watering eye (even if not crying)
- Secondary infection may occur
- Symptoms resolve in 99% of cases by 12 months of age

Blepharitis

Blepharitis is inflammation of the eyelid margins. It may due to meibomian gland dysfunction (common, posterior blepharitis) or seborrhoeic dermatitis/staphylococcal infection (less common, anterior blepharitis). Blepharitis is also more common in patients with rosacea

The meibomian glands secrete oil on to the eye surface to prevent rapid evaporation of the tear film. Any problem affecting the meibomian glands (as in blepharitis) can hence cause drying of the eyes which in turns leads to irritation

Features

- Symptoms are usually bilateral
- Grittiness and discomfort, particularly around the eyelid margins
- Eyes may be sticky in the morning
- Eyelid margins may be red. **Swollen eyelids may be seen in staphylococcal blepharitis**
- Styes and chalazions are more common in patients with blepharitis
- Secondary conjunctivitis may occur

Management

- Softening of the lid margin using hot compresses twice a day
- Mechanical removal of the debris from lid margins - cotton wool buds dipped in a mixture of cooled boiled water and baby shampoo is often used*
- Artificial tears may be given for symptom relief in people with dry eyes or an abnormal tear film

*an alternative is sodium bicarbonate, a teaspoonful in a cup of cooled water that has recently been boiled.

Ocular Manifestations of Rheumatoid Arthritis

Ocular Manifestations of Rheumatoid Arthritis are common, with 25% of patients having eye problems

Scleritis is painful, episcleritis is not painful

Ocular manifestations

- Keratoconjunctivitis sicca (most common)
- Episcleritis (erythema)
- Scleritis (erythema and pain)
- Corneal ulceration
- Keratitis → associated with acns rosacea

Iatrogenic

- Steroid-induced cataracts
- Chloroquine retinopathy

Thyroid eye disease affects between 25-50% of patients with Graves' disease. It is thought to be due to an autoimmune response against an autoantigen, possibly the TSH receptor, causing retro-orbital inflammation. The patient may be eu-, hypo- or hyperthyroid at the time of presentation

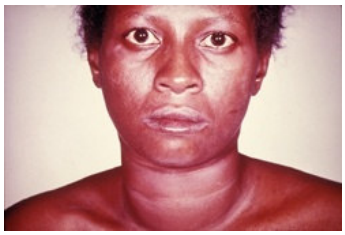
Prevention

- Smoking is the most important modifiable risk factor for the development of thyroid eye disease
- Radioiodine treatment may ↑ the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help ↓ the risk

Exophthalmos ☺

Features

- Exophthalmos
- Conjunctival edema
- Papilledema
- Ophthalmoplegia
- Inability to close the eye lids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy



Exophthalmos

Management

- Topical lubricants may be needed to help prevent corneal inflammation caused by exposure
- Steroids
- Radiotherapy
- Surgery

Herpes Zoster Ophthalmicus (HZO) describes the reactivation of the varicella zoster virus in the area supplied by the ophthalmic division of the trigeminal nerve. It accounts for around 10% of case of shingles.

Features

- Vesicular rash around the eye, which may or may not involve the actual eye itself
- Hutchinson's sign: rash on the tip or side of the nose. Indicates nasociliary involvement and is a strong risk factor for ocular involvement

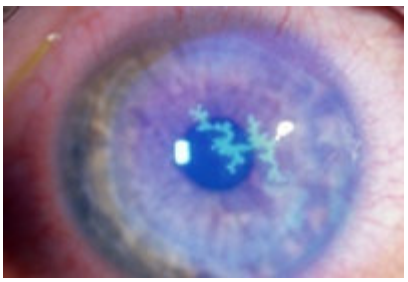
Management

- Oral antiviral treatment for 7-10 days ideally started within 72 hours. Topical antiviral treatment is not given in HZO
- Oral corticosteroids may reduce the duration of pain but do not reduce the incidence of post-herpetic neuralgia
- Ocular involvement requires urgent ophthalmology review

Complications

- Ocular: conjunctivitis, keratitis, episcleritis, anterior uveitis
- Ptosis
- Post-herpetic neuralgia

Herpes Simplex Keratitis most commonly presents with a dendritic corneal ulcer



Features

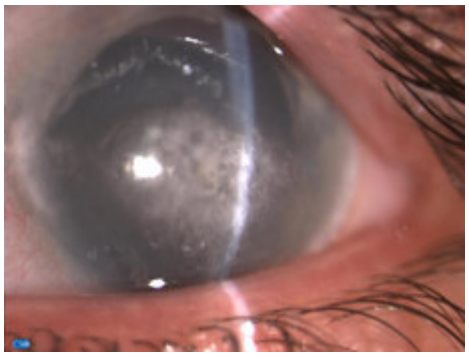
- Red, painful eye
- Photophobia
- Epiphora
- Visual acuity may be ↓
- Fluorescein staining may show an epithelial ulcer, dendritic pattern of staining.

Management

- Immediate referral to an ophthalmologist
- Topical acyclovir

Band keratopathy: is a corneal disease derived from the appearance of calcium on the central cornea caused by calcium deposition in Bowman's layer. This is an example of metastatic calcification, which by definition, occurs in the presence of hypercalcemia

Symptoms include pain and decreased visual acuity.



Treatment: the calcium can be scraped off the cornea or removed with a laser. This can restore sight, but it can take a number of months for normal vision to return as the cornea will be damaged during the operation. This cannot be repeated too many times as it would make the cornea thinner and thinner.

Diabetic Retinopathy is the most common cause of blindness in adults aged 35-65 years-old. Hyperglycemia is thought to cause ↑ retinal blood flow and abnormal metabolism in the retinal vessel walls. This precipitates damage to endothelial cells and pericytes.

Endothelial dysfunction leads to ↑ vascular permeability which causes the characteristic exudates seen on fundoscopy. Pericyte dysfunction predisposes to the formation of microaneurysms. Neovasculization is thought to be caused by the production of growth factors in response to retinal ischemia

Macular Edema

Prevalence	Risk Factors
• 2-6% of background retinopathy • 20-60%preproliferative retinopathy • 70-75% of proliferative cases.	• ↑ HbA1c • Protienuria • Duration of DM

In postgraduate exams you are most likely to be asked about the characteristic features of the various stages/types of diabetic retinopathy. Recently a new classification system has been proprosed, dividing patients into those with non-proliferative diabetic retinopathy (NPDR) and those with proliferative **Retinopathy (PDR):**

Traditional classification	New classification
Background retinopathy • Microaneurysms (dots) • Blots hemorrhages (=3) • Hard exudates Pre-proliferative retinopathy • Cotton wool spots (soft exudates; ischemic nerve fibres) • >3 blots hemorrhages • Venous beading/looping • Deep/dark cluster hemorrhages • More common in type I DM, treat with laser photocoagulation	Mild NPDR • 1 or more microaneurysm Moderate NPDR • Microaneurysms • Blot hemorrhages • Hard exudates • Cotton wool spots, venous beading/looping and intraretinal microvascular abnormalities (IRMA) less severe than in severe NPDR Severe NPDR • Blot hemorrhages and microaneurysms in 4 quadrants • Venous beading in at least 2 quadrants • IRMA in at least 1 quadrant

Proliferative retinopathy → (**urgent referral to an ophthalmologist for panretinal photocoagulation**)

- Retinal neovascularisation - may lead to vitrous hemorrhage
- Fibrous tissue forming anterior to retinal disc
- More common in type I DM, 50% blind in 5 years

Microaneurysm on fluorescein angiography is the earlist sign of DM Nephropathy

Maculopathy

- Based on location rather than severity, anything is potentially serious
- Hard exudates and other 'background' changes on macula
- Check visual acuity
- More common in type II DM

Asymmetric DM Retinopathy → suspect ocular ischemia (carotid artery disease)

Screening

- T1DM
  - Newly diagnosed DM → after 5 years
  - From 5-10 years → anuual
  - More than 10 years DM → 6 monthly
- T2DM
  - Anually

Optic Neuritis:

Causes:

- Multiple sclerosis
- Diabetes
- Syphilis

Features

- Unilateral ↓ in visual acuity over hours or days
- Poor discrimination of colors, 'red desaturation'
- Pain worse on eye movement
- Relative afferent pupillary defect
- Central scotoma

Prognosis

- MRI: if > 3 white-matter lesions, 5-year risk of developing multiple sclerosis is c. 50%

Unilateral decrease in visual acuity over hours or days

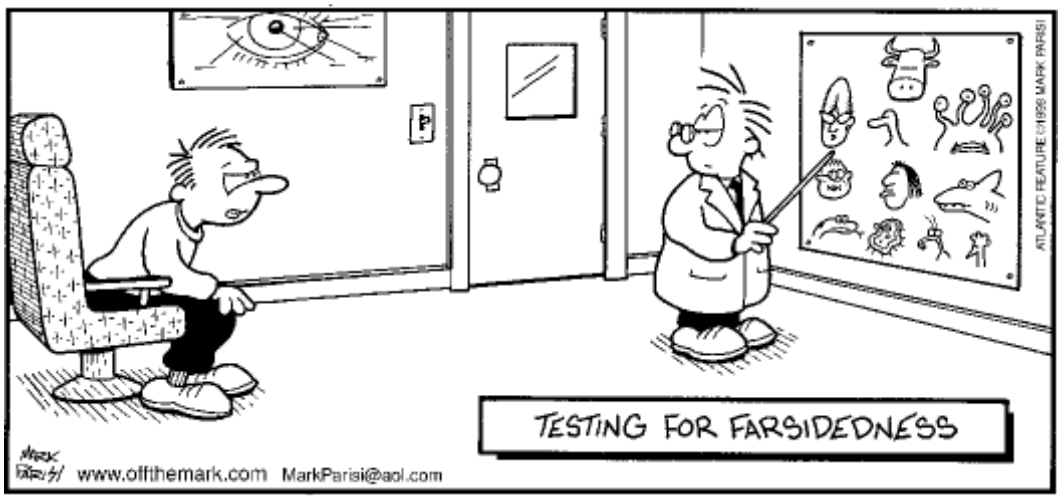
Retrobulbar Neuritis: inflammation behind the optic nerve head, the optic disc is normal.

Patient sees nothing, Doctor sees nothing

Features:

- Visual acuity loss
- Afferent pupillary defect during swinging flashing light
- Color vision will be reduced (red looks pallor)

Trochlear Nerve Palsy: cause torsional diplopia, Torsion is a normal response to tilting the head sideways. The eyes automatically rotate in an equal and opposite direction, so that the orientation of the environment remains unchanged – vertical things remain vertical.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"My goodness, when's the last time anyone checked on Mr. Klink in room 207?!"

PHARMACOLOGY

Drug metabolism
- **phase I: oxidation, reduction, hydrolysis**
- **phase II: conjugation**

Pharmacokinetics: metabolism

Drug metabolism usually involves two types of biochemical reactions - phase I and phase II reactions

- Phase I reactions: oxidation, reduction, and hydrolysis. Mainly performed by the P450 enzymes but some drugs are metabolised by specific enzymes, for example alcohol dehydrogenase and xanthine oxidase. Products of phase I reactions are typically more active and potentially toxic
- Phase II reactions: conjugation. Products are typically inactive and excreted in urine or bile. Glucuronyl, acetyl, methyl, sulphate and other groups are typically involved.
- The majority of phase I and phase II reactions take place in the liver.

First-Pass Metabolism is a phenomenon where the concentration of a drug is greatly ↓ before it reaches the systemic circulation due to hepatic metabolism. As a consequence much larger doses are need orally than if given by other routes. This effect is seen in many drugs, including:

- Aspirin
- Isosorbide dinitrate
- Glyceryl trinitrate
- Lignocaine
- Propranolol
- Verapamil

Zero-Order Kinetics describes metabolism which is independent of the concentration of the reactant. This is due to metabolic pathways becoming saturated resulting in a constant amount of drug being eliminated per unit time. This explains why people may fail a breathalyser test in the morning if they have been drinking the night before

Drugs exhibiting zero-order kinetics

- Phenytoin
- Salicylates
- Heparin
- Ethanol

Drugs affected by **acetylator status:**

- Isoniazid
- Procainamide
- Hydralazine
- Dapsone
- Sulfasalazine

Acetylator Status
50% of the UK population is deficient in hepatic N-acetyltransferase

P-450 Dependent Drugs WEPTD:

- Warfarin
- Estrogen
- Phenytoin
- Theophylline
- Digoxin

P450 inhibtors: (causing low metabolism of WEPTD → Toxicity)

- Acute alcohol intake
- Allopurinol
- Amiodarone
- Cimetidine, omeprazole
- Dapsone
- Imidazoles: ketoconazole, fluconazole
- INH
- Macrolides (Azithro-Clarithro-Erythro mycins)
- Quinolones (ciprofloxacin)
- Quinupristin
- Sodium valproate
- Spironolactones
- SSRIs: fluoxetine, sertraline
- Grapefruit juice (potent inhibitor of the cytochrome P450 enzyme CYP3A4)
- Protease inhibitors (ndinavir, nelfinavir, ritonavir, saquinavir)

Carbamazepine is an inducer of the P450 system. This in turn increases the metabolism of carbamazepine itself - auto-induction

P450 inducers:

- Antiepileptics: phenytoin, carbamazepine (note that valporate is an inhibitor)
- Barbiturates
- Chronic alcohol intake
- Griseofulvin
- Quinidine
- Rifampicin
- **Smoking (affects CYP1A2, reason why smokers require more aminophylline)**
- St John's Wort
- Sulfa drugs
- Tetracycline
- Nevirapine (NNRTI)

Drugs that can be cleared with Hemodialysis - mnemonic: **BLAST**

• **B**arbiturate • **L**ithium • **A**lcohol (inc methanol, ethylene glycol) • **S**alicylates • **T**heophyllines (charcoal hemoperfusion is preferable)	Drugs which cannot be cleared with HD include • Tricyclics • Benzodiazepines (diazepam,midazolam,alprazolam) • Dextropropoxyphene (co-proxamol) • Digoxin, β-blockers

Drugs to avoid in Renal Failure

- Antibiotics: tetracycline, nitrofurantoin
- NSAIDS
- Lithium

Drugs likely to accumulate in renal failure - need dose adjustment

- Most antibiotics including penicillins, cephalosporins, vancomycin, gentamicin, streptomycin
- Digoxin, atenolol
- Methotrexate
- Sulphonylureas
- Furosemide
- Opioids

Drugs relatively safe - use in normal dose

- Antibiotics: erythromycin, rifampicin
- Diazepam
- Warfarin

Drug Induced Impaired Glucose Tolerance

- Thiazides, furosemide (less common)
- Steroids
- Tacrolimus, cyclosporin
- Interferon-α
- Nicotinic acid (vitamin B3)

β-blockers cause a slight impairment of glucose tolerance. They should also be used with caution in diabetics as they can interfere with the metabolic and autonomic responses to hypoglycemia

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Drug induced Liver Disease is generally divided into hepatocellular, cholestatic or mixed. There is however considerable overlap, with some drugs causing a range of changes to the liver

Hepatocellular Picture	Cholestasis (+/- Hepatitis)	Liver Cirrhosis
• Alcohol • Amiodarone • Anti-tuberculosis: isoniazid, rifampicin, pyrazinamide • Halothane • MAOIs • Methyldopa • Paracetamol • Sodium valproate, phenytoin • **Statins**	• Anabolic steroids, testosterones • Antibiotics: flucloxacillin, co-amoxiclav, erythromycin*, nitrofurantoin • **Fibrates** • Oral contraceptive pill • Phenothiazines: chlorpromazine, prochlorperazine • Rarely: nifedipine • Sulphonylureas	• Amiodarone • Methotrexate • Methyldopa

*risk may be ↓ with erythromycin stearate

Drugs Causing Visual Disturbance:

Cataracts

- Steroids

Corneal opacities

- Amiodarone
- Indomethacin

Optic neuritis

- Ethambutol
- Amiodarone
- Metronidazole

Retinopathy

- Chloroquine, quinine

Blue tinge in vision:

- Sildinafil

Yellow-green tinge:

- Digoxin

Sildenafil can cause both blue discoloration and non-arteritic anterior ischemic neuropathy

Drugs Causing Gingival hyperplasia:

- Phenytoin
- Cyclosporin
- Calcium channel blockers (especially nifedipine)

Other causes of gingival hyperplasia include

- Acute myeloid leukemia (myelomonocytic and monocytic types)

Drugs Causing Urticaria: The following drugs commonly cause urticaria:

- Aspirin
- Penicillins
- NSAIDs
- Opiates

Drugs Causing Acute Intermittent Porphyria (AIP)

Drugs which may precipitate attack	Safe Drugs
• Alcohol • Barbiturates • Benzodiazepines • Halothane • Oral contraceptive pill • Sulphonamides	• Paracetamol • Aspirin • Codeine • Morphine • Chlorpromazine • β-blockers • Penicillin • Metformin

Drug Induced Thrombocytopenia (probable immune mediated)

- Heparin
- Abciximab
- NSAIDs; ASA
- Diuretics: furosemide
- Quinine
- Antibiotics: penicillins, sulphonamides, rifampicin
- Anticonvulsants: carbamazepine, valproate

Drug Induced Pancytopenia:

- Cytotoxics
- Antibiotics: trimethoprim, chloramphenicol
- Anti-rheumatoid: gold (sodium aurothiomalate), penicillamine
- Carbimazole*
- Anti-epileptics: carbamazepine
- Sulphonylureas: tolbutamide

*causes both agranulocytosis and pancytopenia

Drug Induced Photosensitivity:

Rash on the forearms and face is typical of a photosensitivity rash

- Thiazides
- Tetracyclines, sulphonamides, ciprofloxacin
- Amiodarone
- NSAIDs e.g. Piroxicam
- Psoralens
- Sulphonylureas

Smoking Cissation Therapy

NICE released guidance in 2008 on the management of smoking cessation. General points include:

- Patients should be offered nicotine replacement therapy (NRT), varenicline or bupropion - NICE state that clinicians should not favour one medication over another
- NRT, varenicline or bupropion should normally be prescribed as part of a commitment to stop smoking on or before a particular date (target stop date)
- Prescription of NRT, varenicline or bupropion should be sufficient to last only until 2 weeks after the target stop date. Normally, this will be after 2 weeks of NRT therapy, and 3-4 weeks for varenicline and bupropion, to allow for the different methods of administration and mode of action. Further prescriptions should be given only to people who have demonstrated that their quit attempt is continuing
- If unsuccessful using NRT, varenicline or bupropion, do not offer a repeat prescription within 6 months unless special circumstances have intervened
- Do not offer NRT, varenicline or bupropion in any combination

NRT	Varenicline	Bupropion
Nicotine replacement therapy	**Nicotinic receptor partial agonist**	**Norepinephrine and dopamine reuptake inhibitor, and nicotinic antagonist**
• Adverse effects include nausea & vomiting, headaches and flu-like symptoms • Nice recommend offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past	• Should be started 1 week before the patien target date to stop • The recommended course of is 12 weeks (but patients should be monitored regularly and treatment only continued if not smoking) • Has been shown in studies to be more effective than bupropion • Nausea is the most common adverse effect. Other include headache, insomnia, abnormal dreams • Varenicline should be used with caution in patients with a history of depression or self-harm. • Contraindicated in pregnancy and breast feeding	• Should be started 1 to 2 weeks before target date. • Small risk of seizures (1: 1,000) • Bupropion should not be prescribed to individuals with epilepsy or other conditions that lower the seizure threshold, such as alcohol or benzodiazepine withdrawal, anorexia nervosa, bulimia, or active brain tumors. It should be avoided in individuals who are also taking MAOIs. When switching from MAOIs to bupropion, it is important to include a washout period of 2 weeks. Also pregnancy and breastfeeding are contraindications.

Salicylate Overdose: a key concept for the exam is to understand that salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis. Early stimulation of the respiratory centre leads to a respiratory alkalosis whilst later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis. In children metabolic acidosis tends to predominate

The mixed respiratory alkalosis and metabolic acidosis in a sweaty, confused patient point towards salicylate overdose. The development of pulmonary edema suggests severe poisoning and is an indication for hemodialysis

Features

- Hyperventilation (centrally stimulates respiration)
- Tinnitus
- Lethargy
- Sweating, pyrexia*
- Nausea/vomiting
- Hyperglycemia and hypoglycemia
- Seizures
- Coma

Treatment

- General (ABC, charcoal)
- Urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary edema with most units now proceeding straight to hemodialysis in cases of severe poisoning
- Hemodialysis

Indications for hemodialysis in salicylate overdose

- **Serum concentration > 700mg/L**
- Metabolic acidosis resistant to treatment
- Acute renal failure
- Pulmonary edema
- Seizures
- Coma

*salicylates cause the uncoupling of oxidative phosphorylation leading to ↓ adenosine triphosphate production, ↑ oxygen consumption and ↑ carbon dioxide and heat production

Paracetamol Overdose:

Management:

- Start N-acetyl cysteine immediately
- Naloxone if there is hypoxia or respiratory depression

King's College Hospital criteria for liver transplantation (paracetamol liver failure) Arterial pH < 7.3, 24 hours after ingestion **OR** all of the following:

- Prothrombin time > 100 seconds
- Creatinine > 300 µmol/l
- Grade III or IV encephalopathy

Intravenous acetylcysteine is indicated for the treatment of paracetamol (acetaminophen) overdose. When paracetamol is taken in large quantities, a minor metabolite called N-acetyl-p-benzoquinone imine (NAPQI) builds up. It is normally conjugated by glutathione, but when taken in excess, the body's glutathione reserves are not sufficient to inactivate the toxic NAPQI. This metabolite is then free

to react with key hepatic enzymes P450*, therefore damaging hepatocytes. For this indication, acetylcysteine acts to augment the glutathione reserves in the body and, together with glutathione, directly bind to toxic metabolites. These actions serve to protect hepatocytes in the liver from NAPQI.

The following patients are at ↑ risk of developing hepatotoxicity following a paracetamol overdose:

- Chronic alcohol excess
- Patients on p450 enzyme inducers (rifampicin, phenytoin, carbamazepine)
- **anorexia nervosa**: ↓ glutathione stores
- HIV

*this explains why there is a lower threshold for treating patients who take P450 inducing medications e.g. phenytoin or rifampicin

Digoxin Toxicity: digoxin is a cardiac glycoside now used mainly in the management of AF.

The half-life of digoxin is around 36-48 hours. This results in a delay before steady plasma levels are seen, it may take a week to start its action

Actions

- ↓ conduction through the atrioventricular node which slows the ventricular rate in atrial fibrillation and flutter
- ↑ the force of cardiac muscle contraction due to inhibition of the Na^+/K^+ ATPase pump

Features

- Generally unwell, lethargy, nausea & vomiting, confusion, YELLOW-GREEN vision
- Arrhythmias (e.g. AV block, bradycardia)

Precipitating factors

- Classically: Hypokalemia*
- Myocardial ischemia
- Hypomagnesemia, acidosis (Hypo pH), Hypercalcemia, Hypernatremia
- Hypoalbuminemia
- Hypothermia
- Hypothyroidism
- Drugs: amiodarone, quinidine, verapamil, spironolactone (compete for secretion in distal convoluted tubule therefore ↓ excretion)

Management

- Digibind
- Correct arrhythmias
- Monitor K^+

Indications for administration of **Digoxin specific Fab Fragment** are:

- Hemodynamic instability
- Life-threatening arrhythmias
- Serum potassium >5 mmol/l in acute toxicity
- Plasma digoxin level >13nmol/l
- Ingestion of more than 10 mg digoxin in adults and 4 mg in children

*Hyperkalemia may also worsen digoxin toxicity

Cyanide may be used in insecticides, photograph development and the production of certain metals. Toxicity results from reversible inhibition of cellular oxidising enzymes

Presentation

- 'Classical' features: BRICK-RED SKIN, smell of bitter almonds
- Acute: hypoxia, hypotension, headache, confusion
- Chronic: ataxia, peripheral neuropathy, dermatitis

Management

- Supportive measures: 100% oxygen
- Definitive: IV dicobalt edetate

Ethylene glycol is a type of alcohol used as a **COOLANT OR ANTIFREEZE**

Ethylene glycol toxicity management - fomepizole. Also ethanol / hemodialysis

Fomepizole is now used first-line rather than ethanol in ethylene glycol toxicity. There is no indication for hemodialysis unless metabolic acidosis occurred or the case is refractory to antidotes

Features of toxicity are divided into 3 stages:

- Stage 1: symptoms similar to alcohol intoxication: confusion, slurred speech, dizziness
- Stage 2: metabolic acidosis with high anion gap and high osmolar gap. Also tachycardia, hypertension
- Stage 3: acute renal failure

Management has changed recently:

- Ethanol has been used for many years
- Works by competing with ethylene glycol for the enzyme alcohol dehydrogenase, this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the hemodynamic/metabolic features of poisoning
- **fomepizole**, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol
- Hemodialysis also has a role in refractory cases

Cocaine use may cause a wide variety of adverse effects

Cardiovascular effects

- Myocardial infarction
- Both tachycardia and bradycardia may occur
- Hypertension
- QRS widening and QT prolongation
- Aortic dissection

Neurological effects

- Seizures
- Hypertonia
- Hyperreflexia

Psychiatric effects

- Agitation
- Psychosis
- Hallucinations

Others

- Hyperthermia
- Metabolic acidosis
- Rhabdomyolysis leading to renal failure.

Ecstasy (MDMA, 3,4-Methylenedioxymeth**amphetamine**) use became popular in the 1990's during the emergence of dance music culture

Clinical features

- Neurological: agitation, anxiety, confusion, ataxia
- Cardiovascular: tachycardia, hypertension
- Water intoxication
- Hyperthermia
- Rhabdomyolysis
- Hyponatremia

Management

- Supportive
- Dantrolene may be used for hyperthermia if simple measures fail

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Mercury Poisoning:

Features

- Paraesthesia
- Visual field defects
- Hearing loss
- Irritability
- Renal tubular acidosis

Chelation therapy for acute inorganic mercury poisoning can be done with DMSA, 2,3-dimercapto-1-propanesulfonic acid (DMPS), D-penicillamine (DPCN), or dimercaprol (BAL). Only DMSA is FDA-approved for use in children for treating mercury poisoning.

However, several studies found no clear clinical benefit from DMSA treatment for poisoning due to mercury vapor. No chelator for methylmercury or ethylmercury is approved by the FDA; DMSA is the most frequently used for severe methylmercury poisoning, as it is given orally, has fewer side effects, and has been found to be superior to BAL, DPCN, and DMPS

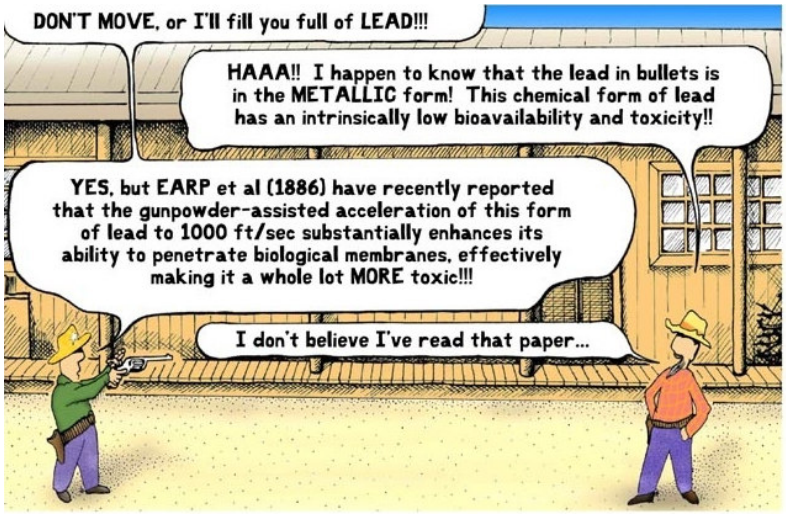
Lead Poisoning: Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of **abdominal pain and neurological signs**

Features

- Abdominal pain
- Peripheral neuropathy (mainly motor)
- Fatigue
- Constipation
- Blue lines on gum margin (only 20% of adult patients, very rare in children)

Investigations

- Microcytic anemia
- Blood film shows red cell abnormalities including basophilic stippling and clover-leaf morphology
- Raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- Urinary coproporphyrin is also ↑ (urinary porphobilinogen and uroporphyrin levels are normal to slightly ↑)



Management - various chelating agents are currently used:

- Dimercaptosuccinic acid (DMSA)
- D-penicillamine
- EDTA (**E**thylene**D**iamine**T**etra**A**cetic acid)
- Dimercaprol

Carbon Monoxide has high affinity for hemoglobin and myoglobin resulting in a left-shift of the oxygen dissociation curve and tissue hypoxia. There are approximately 50 per year deaths from accidental carbon monoxide poisoning in the UK.

Questions may hint at badly maintained housing e.g. student houses

Confusion, pyrexia and pink mucosae are typical features of carbon monoxide poisoning

Features of carbon monoxide toxicity

- Headache: 90% of cases
- Nausea and vomiting: 50%
- Vertigo: 50%
- Confusion: 30%
- Subjective weakness: 20%
- Severe toxicity: 'pink' skin and mucosae, hyperpyrexia, arrhythmias, extrapyramidal features, coma, death

Typical carboxyhemoglobin levels

- < 3% non-smokers
- < 10% smokers
- 10 - 30% symptomatic: headache, vomiting, dizziness
- > 30% severe toxicity:
  - 50-60%: Syncope, tachycardia, fits
  - > 60%: ↑ risk of cardiorespiratory failure and death

Management

- 100% oxygen
- Hyperbaric oxygen

Indications for hyperbaric oxygen

- Loss of consciousness at any point
- Neurological signs other than headache
- Myocardial ischemia or arrhythmia
- Pregnancy

Oculogyric Crisis is a dystonic reaction to certain drugs or medical conditions

Features (extra pyramidal)

- Restlessness, agitation
- Involuntary upward deviation of the eyes

Causes

- Phenothiazines
- Haloperidol
- Metoclopramide
- Postencephalitic Parkinson's disease.

Treatment

- Procyclidine
- Benztropine

Pregnancy and Medications: Very few drugs are known to be completely safe in pregnancy. The list below largely comprises of those known to be harmful. Some countries have developed a grading system

Contraindicated in pregnancy

Drugs	Antibiotics
• ACE inhibitors, ARBs • Statins • Warfarin • Sulfonylureas • Retinoids (including topical) • Cytotoxic agents	• Tetracyclines • Aminoglycosides • Sulphonamides • Trimethoprim • Quinolones: the BNF advises to avoid due to arthropathy in some animal studies

Majority of antiepileptics including valproate, carbamazepine and phenytoin are known to be potentially harmful. Decision to stop such treatments however is difficult as uncontrolled epilepsy is also a risk

Breastfeeding Contraindications: The major breastfeeding contraindications tested in exams relate to drugs (see below). Other contraindications of note include:

- Galactosemia
- Viral infections - this is controversial with respect to HIV in the developing world. This is because there is such an ↑ infant mortality and morbidity associated with bottle feeding that some doctors think the benefits outweigh the risk of HIV transmission

Breast feeding is acceptable with nearly all anti-epileptic drugs

Taken in normal doses, with the possible exception of barbiturates

SAFE	DANGEROUS
• Antibiotics: penicillins, cephalosporins, trimethoprim • Endocrine: glucocorticoids (avoid high doses), levothyroxine* • Epilepsy: sodium valproate, carbamazepine • Asthma: salbutamol, theophyllines • Psychiatric drugs: tricyclic antidepressants, antipsychotics** • Hypertension: β-blockers, hydralazine, methyldopa • Anticoagulants: warfarin, heparin • Digoxin	• Antibiotics: ciprofloxacin, tetracycline, chloramphenicol, sulphonamides • Psychiatric drugs: lithium, benzodiazepines, clozapine • Aspirin • Carbimazole • Sulphonylureas • Cytotoxic drugs • Amiodarone

*the BNF advises that the amount is too small to affect neonatal hypothyroidism screening
**clozapine should be avoided

Heparin can be given as either unfractionated, intravenous heparin, or low molecular weight heparin (LMWH), given subcutaneously. Heparins generally act by activating antithrombin III. Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. LMWH however only ↑ the action of antithrombin III on factor Xa

Heparin overdose may be reversed by protamine sulphate

The table below shows the differences between standard heparin and LMWH:

	Standard Heparin	(LMWH)
Administration	Intravenous	Subcutaneous
Action duration	Short	Long
Mechanism of action	Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, XIa and XIIa	Activates antithrombin III. Forms a complex that inhibits factor Xa
Side-effects	Bleeding HIT Osteoporosis	Bleeding Lower risk of HIT and osteoporosis
Monitoring	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
Notes	Useful in situations where there is a ↑ risk of bleeding as anticoagulation can be terminated rapidly	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

Heparin-induced thrombocytopaenia (HIT)

- Immune mediated - antibodies form which cause the activation of platelets
- Usually does not develop until after 5-10 days of treatment
- Despite being associated with low platelets HIT is actually a prothrombotic condition
- Features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- Treatment options include alternative anticoagulants such as lepirudin and danaparoid

Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

Adrenaline is a sympathomimetic amine with both α and β adrenergic stimulating properties

Adrenaline induced ischemia - phentolamine

Phentolamine, a short acting α blocker, may be used as local infiltration in situations like accidental injection of adrenaline. It is normally used mainly to control blood pressure during surgical resection of Pheochromocytoma.

Indications

- Anaphylaxis
- Cardiac arrest

Recommend Adult Life Support (ALS) adrenaline doses

- **Anaphylaxis: 0.5ml 1:1,000 IM**
- **Cardiac arrest: 10ml 1:10,000 IV or 1ml of 1:1000 IV**

Therapeutic Drug Monitoring

Phenytoin

- Trough levels immediately before dose

Cyclosporin

- Trough levels immediately before dose

Digoxin

- At least 6 hrs post-dose

Lithium

- Range = 0.4 - 1.0 mmol/l
- Take 12 hrs post-dose

PC-DL

Botulinum Toxin ('Botox'): As well as the well publicised cosmetic uses of Botulinum toxin ('Botox') there are also a number of licensed **indications**:

- Blepharospasm
- Hemifacial spasm
- Focal spasticity including cerebral palsy patients, hand and wrist disability associated with stroke
- Spasmodic torticollis
- Severe hyperhidrosis of the axillae
- Achalasia

Isotretinoin is an oral retinoid used in the treatment of severe acne. Two-thirds of patients have a long term remission or cure following a course of oral isotretinoin

Adverse effects

- Teratogenicity: ♀s MUST be using two forms of contraception (e.g. COCP and condoms)
- Dry skin, eyes and lips: the most common side-effect of isotretinoin
- Low mood, depression
- Raised triglycerides
- Hair thinning
- Nose bleeds (caused by dryness of the nasal mucosa)
- Benign intracranial hypertension: isotretinoin treatment should not be combined with tetracyclines for this reason

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Palliative Care Prescribing: SIGN issued guidance on the control of pain in adults with cancer in 2008

Selected points

- The breakthrough dose of morphine is one-sixth the daily dose of morphine
- All patients who receive opioids should be prescribed a laxative
- Opioids should be used with caution in patients with chronic kidney disease. Alfentanil, buprenorphine and fentanyl are preferred
- metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy

Conversion between opioids

From	To	
Oral codeine	Oral morphine	Divide by 10
Oral tramadol	Oral morphine	Divide by 5
Oral morphine	Oral oxycodone	Divide by 2

The BNF states that oral morphine sulphate 80-90mg over 24 hours is approximately equivalent to one '25 mcg/hour' patch, therefore product literature should be consulted

From	To	
Oral morphine	Subcutaneous diamorphine	Divide by 3
Oral oxycodone	Subcutaneous diamorphine	Divide by 1.5

Management of hiccups in palliative care

- Chlorpromazine is licensed for the treatment of intractable hiccups
- Haloperidol, gabapentin and baclofen are also used

In the terminal phase of the illness (Care of the Dying pathway) then agitation or restlessness is best treated with midazolam S/C injection.

Hydrocortisone Equivalence

- 1mg prednisolone = 4mg hydrocortisone
- 1mg dexamethasone = 7mg prednisolone

Chemotherapy Side effects: Nausea and vomiting are common side-effects of chemotherapy. **Risk factors** for the development of symptoms include:

- Anxiety
- Age less than 50 years old
- Concurrent use of opioids
- The type of chemotherapy used

For patients at low-risk of symptoms then drugs such as **metoclopramide** may be used first-line. For high-risk patients then **5HT3 receptor antagonists** such as **ondansetron** are often effective, especially if combined with dexamethasone

Medication overuse headache is one of the most common causes of chronic daily headache. It may affect up to 1 in 50 people

Features

- Present for 15 days or more per month
- Developed or worsened whilst taking regular symptomatic medication
- Patients using opioids and triptans are at most risk
- May be psychiatric co-morbidity

Management

- Simple analgesics and triptans should be withdrawn abruptly (may initially worsen headaches)
- Opioid analgesics should be gradually withdrawn

"Please pass the NaCl."

Doxazosin is an α-1 adrenoceptor antagonist used in the treatment of hypertension and benign prostatic hypertrophy

Adrenoceptor Antagonists

α antagonists

- α-1: doxazosin
- α-1a: tamsulosin - acts mainly on urogenital tract
- α-2: yohimbine
- Non-selective: phenoxybenzamine (previously used in peripheral arterial disease)

β antagonists

- β-1: atenolol
- Non-selective: propranolol

Carvedilol and labetalol are mixed α and β antagonists

Lithium is mood stabilising drug used most commonly prophylatically in bipolar disorder but also as an adjunct in refractory depression. It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys

Lithium: fine tremor in chronic treatment, coarse tremor in acute toxicity

Tricyclic overdose may present with seizures but it does not typical cause a tremor

Mechanism of action - not fully understood, two theories:

- Interferes with inositol triphosphate formation
- Interferes with cAMP formation

Adverse effects

- Nausea/vomiting, diarrhea
- Fine tremor
- Polyuria
- Thyroid enlargement, may lead to hypothyroidism
- ECG: T wave flattening/inversion
- Weight gain

Monitoring of patients on lithium therapy

- Inadequate monitoring of patients taking lithium is common - NICE and the National Patient Safety Agency (NPSA) have issued guidance to try and address this. As a result it is often an exam hot topic
- Lithium blood level should 'normally' be checked every 3 months. Levels should be taken 12 hours post-dose
- Thyroid and renal function should be checked every 6 months
- Patients should be issued with an information booklet, alert card and record book

Lithium toxicity generally occurs following concentrations > 1.5 mmol/L.

Toxicity may be precipitated by dehydration, renal failure, diuretics (Especially bendroflumethiazide) or ACE inhibitors and ARBs

BNF advises that neurotoxicity may be ↑ when lithium is given with diltiazem or verapamil but there is no significant interaction with amlodipine.

Features of toxicity

- Coarse tremor (a fine tremor is seen in therapeutic levels)
- Acute confusion
- Seizure
- Coma

Management

- Mild-moderate toxicity may respond to volume resuscitation with normal saline
- Hemodialysis may be needed in severe toxicity
- Sodium bicarbonate is sometimes used but there is **limited evidence to support this**. By increasing the alkalinity of the urine it promotes lithium excretion.

Tricyclic Antidepressants

Name	Adrenergic uptake inhibitor	Serotonin reuptake inhibitors	Dopamine antagonist	Histamine antagonist
amitriptyline	yes	-	-	-
amoxapine	yes	yes	metabolite	-
clomipramine	-	yes	-	-
desipramine	yes	-	-	-
dothiepin hydrochloride	yes	-	-	-
doxepin	yes	-	-	yes
imipramine	yes	-	-	-
iprindole	yes	-	-	-
lofepramine	yes	-	-	-
nortriptyline	yes	-	-	-
opipramol	yes	-	-	-
protriptyline	yes	-	-	-
trimipramine	Yes	-	-	-

Tricyclic Overdose is a common presentation to A&E departments. Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:

- Arrhythmias
- Seizures
- Metabolic acidosis
- Coma

ECG changes include:

- Sinus tachycardia
- Widening of QRS
- Prolongation of QT interval

Widening of QRS > 100ms is associated with ↑ risk of seizures whilst QRS > 160ms is associated with ventricular arrhythmias

Management

- IV bicarbonate may ↓ the risk of seizures and arrhythmias in severe toxicity
- Arrhythmias: class I-a (e.g. Quinidine) and class I-c antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. **Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias**
- Dialysis is ineffective in removing tricyclics

Phenytoin is associated with a large number of adverse effects. These may be divided into acute, chronic, idiosyncratic and teratogenic

Acute

- Initially: vertigo, diplopia, nystagmus, slurred speech, ataxia
- Later: confusion, seizures

Chronic

- Common: gingival hyperplasia, hirsuitism, coarsening of facial features
- **Megaloblastic anemia (secondary to altered folate metabolism)**
- Peripheral neuropathy
- Enhanced vitamin D metabolism causing osteomalacia
- Lymphadenopathy
- Dyskinesia

Idiosyncratic

- Fever
- Rashes, including severe reactions such as toxic epidermal necrolysis
- Hepatitis
- Dupuytren's contracture (although not listed in the BNF)
- Aplastic anemia
- Drug-induced lupus

Teratogenic

- Associated with cleft palate and congenital heart disease

Sodium Valproate is used in the management epilepsy and is first line therapy for generalised seizures. It works by increasing GABA activity

Adverse effects

- Gastrointestinal: nausea
- ↑ appetite and weight gain
- Alopecia: regrowth may be curly (note that phenytoin → hirsutism while valporate → alopecia)
- Ataxia
- Tremor
- Hepatitis (also with phenytoin)
- Pancreatitis
- Teratogenic

Anticholinesterase Effects: One of the effects of organophosphate poisoning is inhibition of acetylcholinesterase

Features can be predicted by the accumulation of acetylcholine (mnemonic = SLUD)

- Salivation
- Lacrimation
- Urination
- Defecation
- Cardiovascular: hypotension, bradycardia
- Also: small pupils, muscle fasciculation

Management

- Atropine
- The role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit

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St John's Wort: Overview

- Shown to be as effective as tricyclic antidepressants in the treatment of mild-moderate depression
- Mechanism: thought to be similar to SSRIS (although noradrenaline uptake inhibition has also been demonstrated)
- NICE advise 'may be of benefit in mild or moderate depression, but its use should not be prescribed or advised because of uncertainty about appropriate doses, variation in the nature of preparations, and potential serious interactions with other drugs'

Adverse effects

- Profile in trials similar to placebo
- Can cause serotonin syndrome
- Inducer of P450 system, therefore ↓ levels of drugs such as warfarin, Cyclosporin. The effectiveness of the combined oral contraceptive pill may also be ↓

Monoamine Oxidase Inhibitors (MAOIs):

- Serotonin and noradrenaline are metabolised by monoamine oxidase in the presynaptic cell

Non-selective monoamine oxidase inhibitors

- E.g. tranylcypromine, phenelzine
- Used in the treatment of depression and other psychiatric disorder
- Not used frequently due to side-effects

Adverse effects of non-selective monoamine oxidase inhibitors

- Hypertensive crisis: MAOIs reacting with tyramine containing foods e.g. Cheese, pickled herring, Bovril, oxo, marmite, broad beans, liver, wine.
- Anticholinergic effects

Serotonin Receptors Medications: Below is a summary of drugs which are known to act via modulation of the serotonin (5-HT) system. It should be noted that 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis

Agonists

- Sumatriptan is a 5-HT1D receptor agonist which is used in the acute treatment of migraine
- Ergotamine is a partial agonist of 5-HT1 receptors

Antagonists

- Pizotifen is a 5-HT2 receptor antagonist used in the prophylaxis of migraine attacks.
- Methysergide is another antagonist of the 5-HT2 receptor but is rarely used due to the risk of retroperitoneal fibrosis
- Cyproheptadine is a 5-HT2 receptor antagonist which is used to control diarrhea in patients with carcinoid syndrome
- Olanzapine is 5-HT2 antagonist and D2 dopamin receptor blocker, it's an atypical antipsychotic
- Ondansetron and Granisetron are 5-HT3 receptor antagonist and is used as an antiemetic... They cause conistipation, dizziness and headache.

Triptans: are specific 5-HT1 agonists used in the acute treatment of migraine. They are generally used second line when standard analgesics such as paracetamol and ibuprofen are ineffective

Prescribing points

- Should be taken as soon as possible after the onset of headache, rather than at onset of aura
- Oral, orodispersible, nasal spray and subcutaneous injections are available

Adverse effects

- 'Triptan sensations' - tingling, heat, tightness (e.g. Throat and chest), heaviness, pressure

Contraindications

- Patients with a history of, or significant risk factors for ischemic heart disease or cerebrovascular disease

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Dopamine Receptor Agonists:

Indications

- Parkinson's disease
- Prolactinoma/galactorrhoea
- Cyclical breast disease
- Acromegaly

Adverse effects

- Nausea/vomiting
- Postural hypotension
- Hallucinations
- Daytime somnolence

Benzodiazepines antidote is flumazenil

Benzodiazepines enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). They therefore are used for a variety of purposes:

- Sedation
- Hypnotic
- Anxiolytic
- Anticonvulsant
- Muscle relaxant

Patients commonly develop a tolerance and dependance to benzodiazepines and care should therefore be exercised on prescribing these drugs. The Committee on Safety of Medicines advises that benzodiazepines are only prescribed for a short period of time (2-4 weeks).

The BNF gives advice on how to withdraw a benzodiazepine. The dose should be withdrawn in steps of about 1/8 (range 1/10 to 1/4) of the daily dose every fortnight. A suggested protocol for patients experiencing difficulty is given:

- Switch patients to the equivalent dose of diazepam
- Reduce dose of diazepam every 2-3 weeks in steps of 2 or 2.5 mg
- Time needed for withdrawal can vary from 1 month to 1 year or more

If patients withdraw too quickly from benzodiazepines they may experience benzodiazepine withdrawal syndrome, a condition very similar to alcohol withdrawal syndrome. This may occur up to 3 weeks after stopping a long-acting drug. Features include:

- Insomnia
- Irritability
- Anxiety
- Tremor
- Loss of appetite
- Tinnitus
- Perspiration
- Perceptual disturbances
- Seizures

Anti Arrythmias

Class I
Na^+ channel Blocker

IA
↑AP
- Quinidine
- Procinamide
- Disopyramide
- Amiodarone

IB
↓ AP
- Lidocaine
- Mexiletine
- Tocainide
- Phenytoin

IC
- Flecainide
- Ancanide
- Propafenone

Class II
β Blocker

- Propanolol
- Esmolol

Class III
K^+ channel Blocker

- Sotalol
- Bretylium
- Amiodarone

Class IV
Ca^{++} Channel Blocker

- Verapamil
- Diltiazem

Class V

- Adenosine
- Digoxin
- K^+ ions
- Mg ions

Amiodarone is a class III antiarrhythmic agent used in the treatment of both atrial and ventricular tachycardias. The main mechanism of action is by **blocking potassium channels** which inhibits repolarisation and hence prolongs the action potential. Amiodarone also has other actions such as blocking sodium channels (a class I-a effect)

The **use of amiodarone is limited** by a number of factors

- Long half-life (20-100 days)
- Should ideally be given into central veins (causes thrombophlebitis)
- Has proarrhythmic effects due to lengthening of the QT interval
- Interacts with drugs commonly used concurrently e.g. ↓ metabolism of warfarin = P450 inhibtor
- Numerous long-term adverse effects (see below)

Monitoring of patients taking amiodarone

- TFT, LFT, U&E, CXR prior to treatment. **U&E to check hypokalemia**
- TFT, LFT every 6 months

Adverse effects of amiodarone use

- Thyroid dysfunction
- Corneal deposits
- Pulmonary fibrosis/pneumonitis
- Liver fibrosis/hepatitis
- Peripheral neuropathy, myopathy
- Photosensitivity
- 'Slate-grey' appearance

Amiodarone and Thyroid: Around 1 in 6 patients taking amiodarone develop thyroid dysfunction

Amiodarone-induced hypothyroidism (AIH)
The pathophysiology of amiodarone-induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a **Wolff-Chaikoff effect** (an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide)

Amiodarone may be continued if this is desirable

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

	AIT type 1	AIT type 2
Pathophysiology	↑ iodine, ↑ thyroid hormone synthesis	Amiodarone-related destructive thyroiditis
Goitre	Present	Absent
Color Doppler	↑ Blood flow	↓ Blood flow
Management	Carbimazole or potassium perchlorate	Corticosteroids ± Antithyroid

Unlike in AIH, amiodarone should be stopped if possible in patients who develop AIT

Flecainide is a Vaughan Williams class I-c antiarrhythmic. It slows conduction of the action potential by acting as a potent sodium channel blocker. This may be reflected by widening of the QRS complex and prolongation of the PR interval

The Cardiac Arrhythmia Suppression Trial (CAST, 1989) investigated the use of agents to treat asymptomatic or mildly symptomatic premature ventricular complexes (PVCs) post myocardial infarction. The hypothesis was that this would ↓ deaths from ventricular arrhythmias. Flecainide was actually shown to ↑ mortality post myocardial infarction and is therefore contraindicated in this situation.

Indications

- Atrial fibrillation
- SVT associated with accessory pathway e.g. Wolf-Parkinson-White syndrome

Adverse effects

- Negatively inotropic
- Bradycardia
- Proarrhythmic
- Oral paraesthesia
- Visual disturbance

Statins inhibit the action of HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis → Statins: ↓ cholesterol synthesis.

P450 inhibitors ↑ CK and myopathy

Nicotinic acid ↑ HDL levels

Adverse effects

- Myopathy: includes myalgia, myositis, rhabdomyolysis and asymptomatic raised creatine kinase. Risks factors for myopathy include advanced **age, ♀, low BMI** and presence of **multisystem disease** such as diabetes mellitus. Myopathy is more common in lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (rosuvastatin, pravastatin, fluvastatin)
- Liver impairment: 2008 NICE guidelines recommend checking LFTs at baseline, 3 months and 12 months. Treatment should be discontinued if serum transaminase concentrations rise to and persist at 3 times the upper limit of the reference range

Who should receive a statin?

- All people with established cardiovascular disease (stroke, TIA, IHD, peripheral arterial disease)
- NICE recommend anyone with a 10-year cardiovascular risk = 20%
- The management of blood lipids in type 2 diabetes mellitus (T2DM) has changed slightly. Previously all patients with T2DM > 40-years-old were prescribed statins. Now patients > 40-years-old who have no obvious cardiovascular risk (e.g. Non-smoker, not obese, normotensive etc) and have a cardiovascular risk < 20%/10 years do not need to be given a statin.

Statins should be taken at night as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life than other statins

Current guidelines for lipid lowering**

	Total cholesterol (mmol/l)	LDL cholesterol
Joint British Societies	< 4.0	< 2.0
National Service Framework for CHD	< 5.0	< 3.0
SIGN 2007	< 5.0	< 3.0

**current NICE guidelines do not recommend target cholesterol in primary prevention

The following table compares the side-effects of drugs used in hyperlipidemia:

Drugs	Adverse effects
Statins (HMG CoA reductase inhibitors)	Myositis, deranged LFTs
Ezetimibe	Headache
Nicotinic acid	Flushing, myositis
Fibrates	Myositis, pruritus, cholestasis
Anion-exchange resins	GI side-effects

Both fibrates and nicotinic acid have been associated with myositis, especially when combined with a statin. However, the Committee on Safety of Medicines has produced guidance which specifically warns about the concomitant prescription of fibrates with statins in relation to muscle toxicity

Nicotinic Acid is used in the treatment of patients with hyperlipidemia, although its use is limited by side-effects. As well as lowering cholesterol and triglyceride concentrations it also raises HDL levels

Adverse effects

- Flushing
- Impaired glucose tolerance
- Myositis

β-blocker overdose management: atropine + glucagon

Glucagon has a positive inotropic action on the heart and ↓ renal vascular resistance. It is therefore useful in patients with β-blocker cardiotoxicity

Cardiac pacing should be reserved for patients unresponsive to pharmacological therapy

β-Blocker Cardiotoxicity

Features

- Bradycardia
- Hypotension
- Heart failure
- Syncope

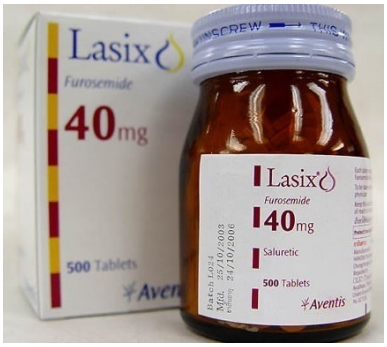
Management

- If bradycardic then atropine
- In resistant cases glucagon may be used
- Hemodialysis is not effective in β-blocker overdose

Furosemide is a loop diuretic that acts by **inhibiting chloride absorption in the ascending loop of Henle**. The name of Lasix is derived from **las**ts **six** (hours) referring to its duration of action.

Adverse effects

- **Hyponatremia**
- **Hypokalemia**
- **Hypocalcaemia**
- **Hypochloraemic alkalosis (Hyper pH)**
- Ototoxicity
- Renal impairment (from dehydration + direct toxic effect)
- **Hyperglycaemia** (less common than thiazides)
- Gout



Bendroflumethiazide (bendrofluazide) is a thiazide diuretic which works by **inhibiting sodium absorption at the beginning of the distal convoluted tubule (DCT).** Potassium is lost as a result of more sodium reaching the collecting ducts. Bendroflumethiazide has a role in the treatment of mild heart failure although loop diuretics are better for reducing overload. The main use of bendroflumethiazide currently is in hypertension (part of the effect is due to vasodilation)

Bendroflumethiazide - mechanism of Hypokalemia:

- ↑ sodium reaching the collecting ducts
- Activation of the renin-angiotensin-aldosterone

Common adverse effects

- Dehydration
- Postural hypotension
- Hyponatremia, Hypokalemia, Hypercalcemia
- Gout
- Impaired glucose tolerance, Hyperglycaemia
- Impotence

Rare adverse effects

- Thrombocytopenia
- Agranulocytosis
- Photosensitivity rash
- Pancreatitis

Spironolactone is an **aldosterone antagonist which acts act in the distal convoluted tubule**

Indications

- Ascites: patients with cirrhosis develop a secondary hyperaldosteronism. Relatively large doses such as 100 or 200mg are often used
- Heart failure (see RALES study below)
- Nephrotic syndrome
- Conn's syndrome

Adverse effects

- Hyperkalemia
- Gynaecomastia

RALES STUDY

- NYHA III + IV, patients already taking ACE inhibitor
- Low dose spironolactone ↓ all cause mortality

Adenosine: The effects of adenosine are enhanced by dipyridamole (anti-platelet agent) and blocked by theophyllines. It should be avoided in asthmatics due to possible bronchospasm.

Adenosine

- Dipyridamole enhances effect
- Aminophylline ↓ effect

Mechanism of action

- Causes transient heart block in the AV node
- Agonist of the A1 receptor which inhibits adenylyl cyclase thus reducing cAMP and causing hyperpolarization by increasing outward potassium flux
- Adenosine has a very short half-life of about 8-10 seconds

Adverse effects

- Chest pain
- Bronchospasm
- Can enhance conduction down accessory pathways, resulting in ↑ ventricular rate (e.g. WPW)

Calcium channel blockers - side-effects: headache, flushing, ankle edema

Calcium channel blockers are primarily used in the management of cardiovascular disease. Voltage-gated calcium channels are present in myocardial cells, cells of the conduction system and those of the vascular smooth muscle. The various types of calcium channel blockers have varying effects on these three areas and it is therefore important to differentiate their uses and actions

Mode of action

- ↓ calcium entry to smooth and cardiac muscle which in turn results in a ↓ force of contraction and slower heart rate

Indications

- Angina, hypertension, arrhythmias (e.g. Narrow complex tachycardia), raynaud's

Dihydropyridines (e.g. nifedipine, amlodipine)

- Effects peripheral circulation i.e. Used for hypertension, raynaud's
- May bring on angina due to sympathetic reflex following vasodilation
- Side-effects: headache, flushing, ankle edema

Verapamil, Diltiazem

- Contraindications: heart failure, heart block, on β-blockers
- Side-effects: headache, constipation, heart block

Ca Channel Blocker	Indications & Notes	SE / CI
Verapamil	Angina, hypertension, arrhythmias Highly negatively inotropic Should not be given with beta-blockers as may cause heart block	Heart failure, constipation, hypotension, bradycardia
Diltiazem	Angina, hypertension Less negatively inotropic than verapamil but caution should still be exercised when patients have heart failure or are taking beta-blockers	Hypotension, bradycardia, heart failure, ankle swelling
Nifedipine, amlodipine, felodipine (dihydropyridines)	Hypertension, angina, Raynaud's Affects the peripheral vascular smooth muscle more than the myocardium and therefore do result in worsening of heart failure (but not amlodepine)	Flushing, headache, ankle swelling

Aspirin works by blocking the action of both cyclooxygenase-1 and 2.

Cyclooxygenase is responsible for prostaglandin, prostacyclin and thromboxane synthesis. The **blocking of thromboxane A2** formation in platelets reduces the ability of platelets to aggregate which has lead to the widespread use of low-dose aspirin in cardiovascular disease. All patients with established cardiovascular disease should take aspirin if there is no contraindication.

Two recent trials (the Aspirin for Asymptomatic Atherosclerosis and the Antithrombotic Trialists Collaboration) have cast doubt on the use of aspirin in primary prevention of cardiovascular disease. Guidelines have not yet changed to reflect this. However the Medicines and Healthcare products Regulatory Agency (MHRA) issued a drug safety update in January 2010 reminding prescribers that aspirin is not licensed for primary prevention.

ASA can be continued normally if patient is going for dental procedure

Who should receive aspirin according to the current guidelines?

- All people with established cardiovascular disease (stroke, TIA, IHD, peripheral arterial disease)
- All people aged 50 years and over with a 10-year cardiovascular risk = 20%
- All people with diabetes mellitus (type 1 or 2) who are = 50 years old or who have: diabetes > 10 years, taking treatment for hypertension or evidence of target organ damage
- All people with target organ damage from hypertension

Potentiates

- Oral hypoglycaemics
- Warfarin
- Steroids

Angiotensin-converting enzyme (ACE) inhibitors are now the established first-line treatment in younger patients with hypertension and are also extensively used to treat heart failure. They are known to be less effective in treating hypertensive Afro-Caribbean patients. ACE inhibitors are also used to treat diabetic nephropathy and have a role in secondary prevention of IHD.

Mechanism of action:

- Inhibit the conversion angiotensin I to angiotensin II

Side-effects:

- Cough: occurs in around 15% of patients and may occur up to a year after starting treatment. Thought to be due to increased bradykinin levels
- Angioedema: may occur up to a year after starting treatment
- Hyperkalaemia
- 1st-dose hypotension: more common in patients taking diuretics

Cautions and contraindications

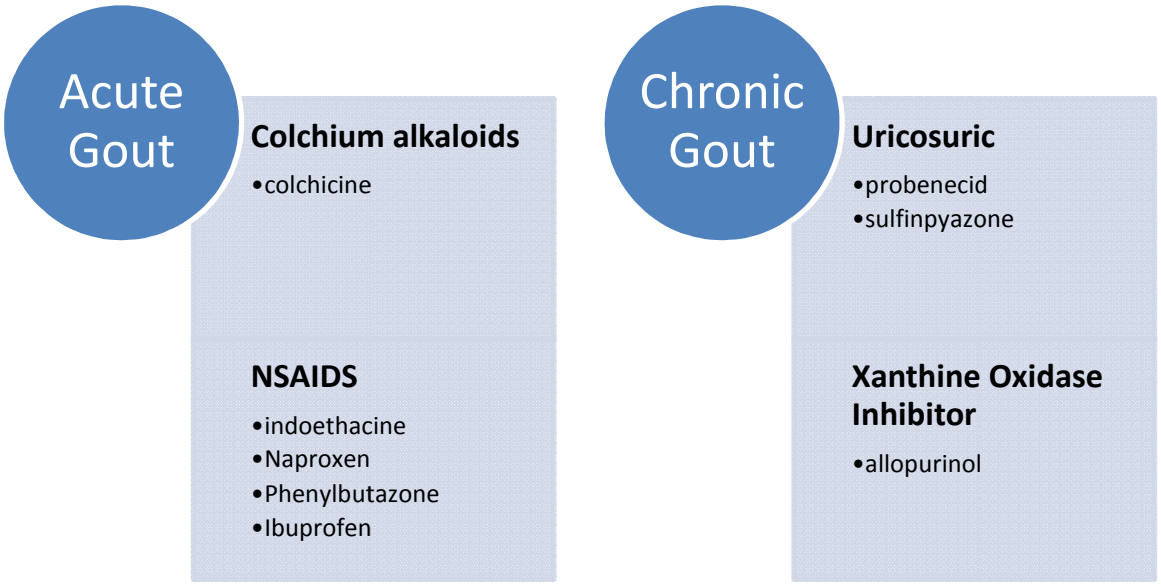
- Pregnancy and breastfeeding - avoid
- Renovascular disease - significant renal impairment may occur in patients who have undiagnosed bilateral renal artery stenosis
- Aortic stenosis - may result in hypotension
- Patients receiving high-dose diuretic therapy (more than 80 mg of furosemide a day) - signficantly increases the risk of hypotension
- Hereditary of idiopathic angioedema

Monitoring

- Urea and electrolytes should be checked before treatment is initiated and after increasing dose
- A rise in the creatinine and potassium may be expected after starting ACE inhibitors. Acceptable increases are an increase in serum creatinine, up to 50% from baseline or up to 265 µmol/l (whichever is smaller) and an increase in potassium up to 5.5 mmol/l.

"It's tough being married to a doctor. I tell him I have a headache and he prescribes sex."

Anti-Gout Medications



Allopurinol is used in the prevention of gout. It works by inhibiting xanthine oxidase which is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid

Initiating allopurinol prophylaxis - see indications below

- **Allopurinol should not be started until 2 weeks after an acute attack has settled**
- Initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300 µmol/l
- NSAID or colchicine cover should be used when starting allopurinol

Indications for allopurinol

- Recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- Tophi
- Renal disease
- Uric acid renal stones
- Prophylaxis if on cytotoxics or diuretics
- Patients with Lesch-Nyhan syndrome often take allopurinol for life

Interactions

Azathioprine

- Metabolised to active compound 6-mercaptopurine
- Xanthine oxidase is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid
- Allopurinol can therefore lead to high levels of 6-mercaptopurine
- A much ↓ dose (e.g. 25%) must therefore be used if the combination cannot be avoided

Cyclophosphamide

- Allopurinol ↓ renal clearance, therefore may cause marrow toxicity

Hormone Replacement Therapy (HRT) involves the use of a small dose of estrogen combined with a progestogen in (women with a uterus) to help alleviate menopausal symptoms.

The indications for HRT have changed significantly over the past ten years as the long-term risks became apparent, primarily as a result of the Women's Health Initiative (WHI) study.

Indications

- Vasomotor symptoms such as flushing, insomnia and headaches
- Premature menopause: should be continued until the age of 50 years
- Osteoporosis: but should only be used as second-line treatment

The main indication is the control of vasomotor symptoms. The other indications such as reversal of vaginal atrophy and prevention of osteoporosis should be treated with other agents as first-line therapies. Other benefits include **↓ incidence of colorectal cancer**

Side-effects

- Nausea
- Breast tenderness
- Fluid retention and weight gain

Potential complications

- ↑ Risk of breast cancer: ↑ by the addition of a progestogen
- ↑ Risk of venous thromboembolism: ↑ by the addition of a progestogen
- ↓ Risk of endometrial cancer: ↓ by the addition of a progestogen but not eliminated completely. The BNF states that the additional risk is eliminated if a progestogen is given continuously

Combined OCP:
↑ Risk of breast cancer
↑ Risk of DVT
↓ Risk of endometrial ca.

Breast cancer

- In the Women's Health Initiative (WHI) study there was a relative risk of 1.26 at 5 years of developing breast cancer
- The ↑ risk relates to duration of use
- Breast cancer incidence is higher in women using combined preparations compared to estrogen-only preparations
- The risk of breast cancer begins to decline when HRT is stopped and by 5 years it reaches the same level as in women who have never taken HRT

Combined Oral Contraceptive Pill: The decision of whether to start a woman on the combined oral contraceptive pill is now guided by the UK Medical Eligibility Criteria (UKMEC). This scale categorises the potential cautions and contraindications according to a four point scale, as detailed below:

- UKMEC 1: a condition for which there is no restriction for the use of the contraceptive method
- UKMEC 2: advantages generally outweigh the disadvantages
- UKMEC 3: disadvantages generally outweigh the advantages
- UKMEC 4: represents an unacceptable health risk

Examples of UKMEC 3 conditions include

- More than 35 years old and smoking less than 15 cigarettes/day
- BMI 35-39 kg/m^2
- Migraine without aura and more than 35 years old
- Family history of thromboembolic disease in first degree relatives < 45 years
- Controlled hypertension
- Breast feeding 6 weeks - 6 months postpartum

Examples of UKMEC 4 conditions include

- More than 35 years old and smoking more than 15 cigarettes/day
- BMI > 40 kg/ m^2
- Migraine with aura
- History of thromboembolic disease or thombogenic mutation
- History of stroke or ischemic heart disease
- Uncontrolled hypertension
- Breast cancer
- Major surgery with prolonged immobilisation

Diabetes mellitus diagnosed > 20 years ago is classified as UKMEC 3 or 4 depending on severity

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Tamoxifen is a selective estrogen receptor modulator (SERM) which acts as an estrogen receptor antagonist and partial agonist. It is used in the management of estrogen receptor positive breast cancer

Adverse effects

- Hot flushes
- Menstrual disturbance: vaginal bleeding, amenorrhoea
- Venous thromboembolism
- Endometrial cancer
- Alopecia
- Cataracts

Raloxifene is a pure estrogen receptor antagonist, and carries a lower risk of endometrial cancer

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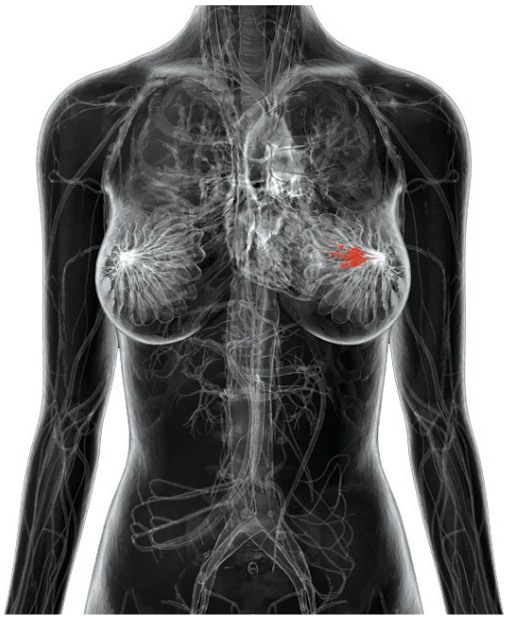

Warfarin - clotting factors affected mnemonic - 1972 (10, 9, 7, 2)

Warfarin is an oral anticoagulant which inhibits the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the formation of clotting factor II, VII, IX and X (mnemonic = 1972) and protein C

P450 inhibitors ↑ INR

INR also ↑ by ABX that kill intestinal flora by ↓ Vit K absorption

Dentistry in warfarinised patients - check INR 72 hours before procedure, proceed if INR < 4.0

If patient has unstable INR then it should be checked 24H prior to procedure

Factors that may potentiate warfarin

- Liver disease
- P450 enzyme inhibitors, e.g.: amiodarone, ciprofloxacin
- Cranberry juice
- Drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- Inhibit platelet function: NSAIDs

Side-effects

- Hemorrhage
- Teratogenic
- Skin necrosis: when warfarin is first started biosynthesis of protein C is ↓. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis

Warfarin overdose:

The following is based on the BNF guidelines, which in turn take into account the British Committee for Standards in Hematology (BCSH) guidelines. A 2005 update of the **BCSH guidelines emphasised the preference of prothrombin complex concentrate over FFP** in major bleeding

Major bleeding	Stop warfarin Vitamin K 5mg IV Prothrombin complex concentrate - if not available then FFP*
INR > 8.0 **No bleeding or minor bleeding**	Stop warfarin, restart when INR < 5.0 If risk factors for bleeding then give vitamin K 0.5mg IV or 5mg PO. Risk factors include: • Age > 70 years • First year of warfarin therapy • History of gastrointestinal bleeding • Hypertension • Alcohol excess Dose can be repeated after 24 hours if INR still high
INR 6.0 - 8.0 **No bleeding or minor bleeding**	Stop warfarin, restart when INR < 5.0

*as FFP can take time to defrost prothrombin complex concentrate should be considered in cases of intracranial hemorrhage

Antivirals

AntiViral	About
Acyclovir	Acyclovir is phosphorylated by thymidine kinase which in turn **inhibits the viral DNA polymerase**
Ribavirin	• Effective against a range of DNA and RNA viruses • Interferes with the **capping of viral mRNA**
Interferons	Inhibit synthesis of mRNA, translation of viral proteins, viral assembly and release
Amantadine	• Used to treat influenza • Inhibits uncoating of virus in cell
Anti-retroviral agent used in HIV	
Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI)	Examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine
Protease inhibitors (PI)	• Inhibits a protease needed to make virus able to survive outside the cell • Examples: indinavir, nelfinavir, ritonavir, saquinavir
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	examples: nevirapine, efavirenz

HIV: Anti-Retrovirals: Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both ↓ viral replication and also ↓ the risk of viral resistance emerging

HIV: anti-retrovirals - P450 interaction
- **nevirapine (NNRTI): induces P450**
- **protease inhibitors: inhibits P450**

Anti-retroviral therapy has previously been delayed until CD4 counts were below 200 * 10^6/l. This was largely due to the toxicity of drugs and fear of resistance developing. Recent guidelines now suggest starting treatment when counts drop below 350 * 10^6/l

Start anti-retrovirals in HIV when CD4 < 350 * 10^6/l

Nucleoside analogue reverse transcriptase inhibitors (NRTI)
- Examples: zidovudine (azt), didanosine, lamivudine, stavudine, zalcitabine
- General NRTI side-effects: peripheral neuropathy
- Zidovudine: anemia, myopathy, black nails
- Didanosine: pancreatitis

Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Examples: nevirapine, efavirenz
- Side-effects: p450 enzyme interaction (nevirapine induces), rashes

Protease inhibitors (PI)
- Examples: indinavir, nelfinavir, ritonavir, saquinavir
- Side-effects: diabetes, hyperlipidemia, buffalo hump, central obesity, p450 enzyme inhibition
- Indinavir: renal stones, asymptomatic hyperbilirubinemia
- Ritonavir: a potent inhibitor of the p450 system

Cyclosporin: is an immunosuppressant which ↓ clonal proliferation of T cells by reducing IL-2 release. It acts by binding to cyclophilin forming a complex which inhibits calcineurin, a phosphotase that activates various transcription factors in T cells

Cyclosporin + tacrolimus - MOA: inhibit calcineurin thus decreasing IL-2

Adverse effects of Cyclosporin

- Nephrotoxicity
- Hepatotoxicity
- Fluid retention
- Tremor
- Hypertension
- Hyperkalemia
- Hypertrichosis
- Hyperplasia of gum
- Impaired glucose tolerance, hyperglycemia.

Indications

- Crohn's disease
- Rheumatoid arthritis
- Psoriasis (has a direct effect on keratinocytes as well as modulating T cell function)
- Following organ transplantation
- Pure red cell aplasia

Tacrolimus is a macrolide antibiotic and is used as an immunosuppressant to prevent transplant rejection. It has a very similar action to Cyclosporin; the action of tacrolimus differs in that it binds to a protein called FKBP rather than cyclophilin

Tacrolimus is more potent than Cyclosporin and hence the incidence of organ rejection is less. However, nephrotoxicity and impaired glucose tolerance is more common

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Azathioprine is metabolised to the active compound mercaptopurine, **purine synthesis inhibitor**, inhibiting the proliferation of cells, especially leukocytes/lymphocytes. It is an effective drug used alone in certain autoimmune diseases, or in combination with other immunosuppressants in organ transplantation. Caution should be exercised when it is used in conjunction with purine analogues such as allopurinol, you may give only 25% of the usual dose of azathioprine. Thiopurine methyltransferase (TPMT) deficiency is present in about 1 in 200 people and predisposes to azathioprine related pancytopaenia. A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity

Adverse effects include

- Bone marrow depression
- Nausea/vomiting
- Pancreatitis

Methotrexate is an antimetabolite which inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines

Indications

- Rheumatoid arthritis
- Psoriasis
- Acute lymphoblastic leukaemia

Adverse effects

- Mucositis
- Myelosuppression
- Pneumonitis
- Liver cirrhosis

Pregnancy

- Men and women should avoid pregnancy for at least 3 months after treatment has stopped

Prescribing methotrexate

- Methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- Methotrexate is taken weekly, rather than daily
- FBC, U&E and LFTs need to be regularly monitored. The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'
- Folic acid 5mg once weekly should be coprescribed, taken more than 24 hours after methotrexate dose
- The starting dose of methotrexate is 7.5 mg weekly
- Only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- Avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia

Drug	MOA
Mycophenolate mofetil	inhibits inosine monophosphate dehydrogenase
Azathioprine	metabolised to the active compound mercaptopurine a purine analogue that inhibits DNA synthesis. **purine synthesis inhibitor**
Methotrexate	antimetabolite which inhibits dihydrofolate reductase

Rituximab:

Uses:

- Non- Hodgkin's lymphoma
- Rheumatoid arthritis in refractory rheumatoid disease
- Used off-label to treat difficult cases of multiple sclerosis, SLE and autoimmune anemias
- Pure red cell aplasia, ITP, Evans syndrome, vasculitis.

Side effects:

- Flu-like illness
- ↓BP during fever
- Tumor side pain

Finasteride is an inhibitor of 5-α-reductase, an enzyme which metabolises testosterone into dihydrotestosterone. Its **indications** are:

- Benign prostatic hyperplasia
- ♂-pattern baldness

Adverse effects:

- Impotence
- ↓ libid
- Ejaculation disorders
- Gynaecomastia and breast tenderness

Finasteride causes ↓ levels of serum prostate specific antigen

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Bisphosphonates are analogues of pyrophosphate, a molecule which ↓ demineralisation in bone. They inhibit osteoclasts by reducing recruitment and promoting apoptosis

Bisphosphonates (alendronate) can cause a variety of esophageal problems

Whilst the development of any new problem following the introduction of a new drug warrants medical review it is particularly important to warn patients starting bisphosphonates about symptoms which could suggest an esophageal reaction, especially with alendronate

Clinical uses

- Prevention and treatment of osteoporosis
- Hypercalcemia
- Paget's disease
- Pain from bone metatases

Adverse effects

- Esophageal reactions: oesophagitis, esophageal ulcers (especially alendronate)
- Osteonecrosis of the jaw
- MHRA has warned about an increased risk of atypical stress fractures of the proximal femoral shaft in patients taking alendronate

The BNF suggests the following counselling for patients taking oral bisphosphonates

- 'Tablets should be swallowed whole with plenty of water while sitting or standing; to be given on an empty stomach at least 30 minutes before breakfast (or another oral medication); patient should stand or sit upright for at least 30 minutes after taking tablet'

Sildenafil is a phosphodiesterase type V inhibitor used in the treatment of impotence

Viagra - contraindicated by nitrates and nicorandil

Nicorandil has a nitrate component as well as being a potassium channel activator
The BNF recommends avoiding α-blockers for 4 hours after sildenafil

Contraindications

- Patients taking nitrates and related drugs such as nicorandil
- Hypotension
- Recent stroke or myocardial infarction
- Non-arteritic anterior ischemic optic neuropathy

Adverse effects

- Visual disturbances e.g. Blue discoloration, non-arteritic anterior ischemic neuropathy
- Nasal congestion
- Flushing
- Gastrointestinal side-effects

Octreotide:

Overview

- Long-acting analogue of somatostatin
- Somatostatin is release from D cells of pancreas and inhibits the release of growth hormone

Uses

- Acute treatment of variceal hemorrhage
- Acromegaly
- Carcinoid syndrome
- Prevent complications following pancreatic surgery
- VIPomas

Adverse effects

- Gallstones (secondary to biliary stasis)

Theophylline, like caffeine, is one of the naturally occurring methylxanthines. The main use of theophyllines in clinical medicine is as a bronchodilator in the management of asthma and COPD

The exact mechanism of action has yet to be discovered. One theory suggests theophyllines may be a non-specific inhibitor of phosphodiesterase resulting in ↑ cAMP. Other proposed mechanisms include antagonism of adenosine and prostaglandin inhibition

Theophylline poisoning features:

- Acidosis, Hypokalemia
- Vomiting
- Tachycardia, arrhythmias
- Seizures

Management

- Activated charcoal
- Charcoal hemoperfusion is preferable to hemodialysis

BTW theophyllines are phosphodiesterase inhibitors while sildenafil is phosphodiesterase type V inhibitor

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Alcohol Withdrawal

Mechanism

- Chronic alcohol consumption enhances GABA mediated inhibition in the CNS (similar to benzodiazepines) and inhibits NMDA-type glutamate receptors
- Alcohol withdrawal is thought to lead to the opposite (↓ inhibitory GABA and ↑ NMDA glutamate transmission)

Features

- Symptoms start at 6-12 hours
- Peak incidence of seizures at 36 hours
- Peak incidence of delirium tremens is at 72 hours

Management

- Benzodiazepines
- Carbamazepine also effective in treatment of alcohol withdrawal
- Phenytoin is said not to be as effective in the treatment of alcohol withdrawal seizures

Proton Pump Inhibitors (PPI) are a group of drugs which profoundly ↓ acid secretion in the stomach. They irreversibly block the hydrogen/potassium adenosine triphosphatase enzyme system (the $H+/K^+$ ATPase) of the gastric parietal cell. Examples include omeprazole and lansoprazole.

Aminosalicylates: 5-aminosalicyclic acid (5-ASA) is released in the colon and is not absorbed. It acts locally as an anti-inflammatory. The mechanism of action is not fully understood but 5-ASA may inhibit prostaglandin synthesis

Sulphasalazine

- A combination of sulphapyridine (a sulphonamide) and 5-ASA
- Many side-effects are due to the sulphapyridine moiety: rashes, **oligospermia**, headache, Heinz body anemia
- Other side-effects are common to 5-ASA drugs (see mesalazine)

Mesalazine

- A delayed release form of 5-ASA
- Sulphapyridine side-effects seen in patients taking sulphasalazine are avoided
- Mesalazine is still however associated with side-effects such as GI upset, diarrhea, headache, agranulocytosis, **pancreatitis***, interstitial nephritis

Olsalazine

- Two molecules of 5-ASA linked by a diazo bond, which is broken by colonic bacteria

*pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

Immunoglobulins: Therapeutics

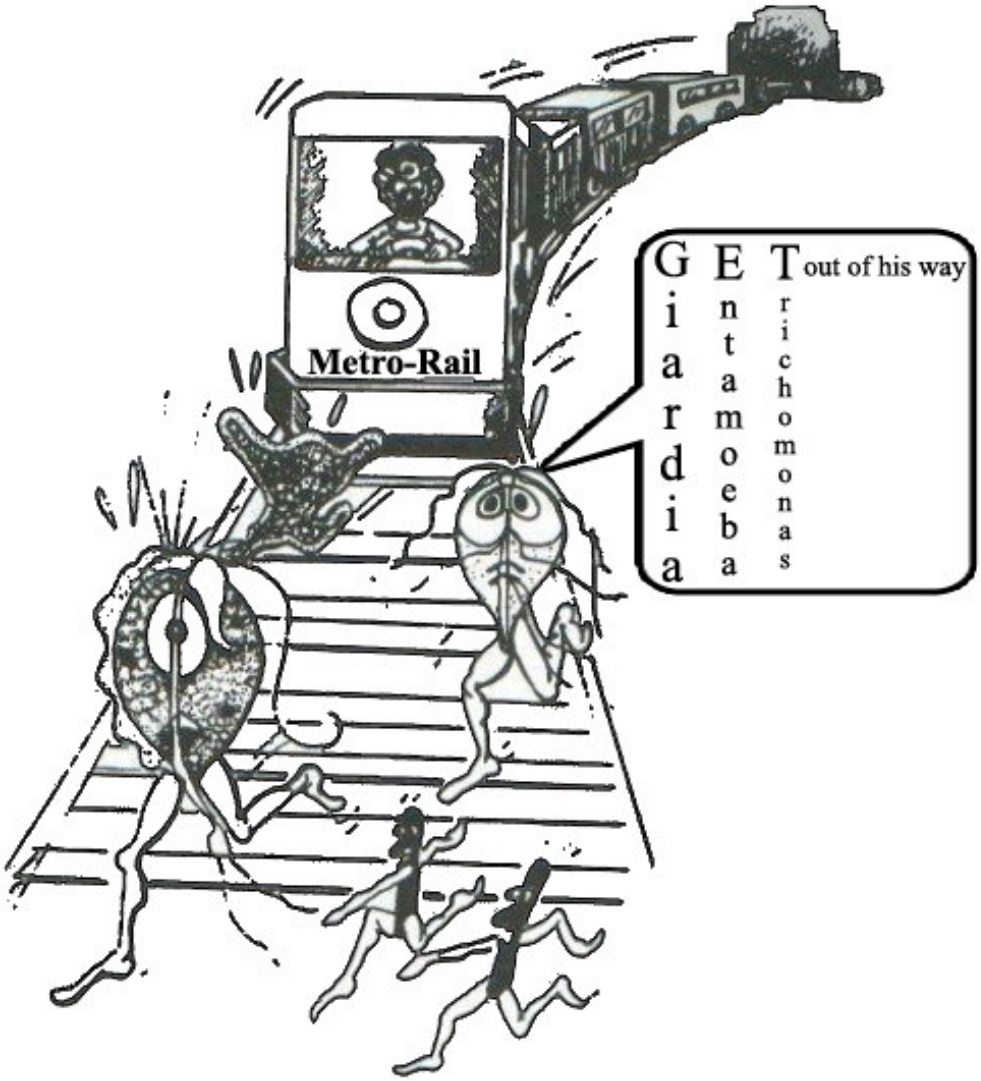
The Department of Health issued guidelines on the use of intravenous immunoglobulins in May 2008

Uses

- Primary and secondary immunodeficiency
- Idiopathic thrombocytopenic purpura (ITP)
- Myasthenia gravis
- Guillain-Barre syndrome
- Kawasaki disease
- Toxic epidermal necrolysis (TEN)
- Pneumonitis induced by CMV following transplantation
- Low serum IgG levels following hematopoietic stem cell transplant for malignancy
- Dermatomyositis
- Chronic inflammatory demyelinating polyradiculopathy

Basics

- Formed from large pool of donors (e.g. 5,000)
- IgG molecules with a subclass distribution similar to that of normal blood
- Half-life of 3 weeks



METROnidazole

Flagyl is named so because it runs after flagellated organisms

ANTIBIOTICS

Inhibit cell wall formation	Inhibit protein synthesis	Inhibit DNA synthesis	Inhibit RNA synthesis
•Penicillins •Cephalosporins •Isoniazid •Vancomycin	•aminoglycosides (cause misreading of mRNA) •chloramphenicol •macrolides (e.g. erythromycin) •tetracyclines •fusidic acid •(Quin/Dalfo)pristin •Linezolid	•quinolones (e.g. ciprofloxacin) •metronidazole •sulphonamides •trimethoprim	•rifampicin

Bactericidal antibiotics

- Penicillins
- Cephalosporins
- Isoniazid
- Aminoglycosides
- Quinupristin+Dalfopristin (combination)
- Metronidazole
- Quinolones: ciprofloxacin, levofluxacin
- Rifampicin
- Nitrofurantoin → Damages bacterial DNA

Bacteriostatic antibiotics

- Chloramphenicol
- Macrolides
- Tetracyclines
- Fusidic acid
- Quinupristin
- Dalfopristin
- Linezolid
- Sulphonamides
- Trimethoprim

Macrolides:

- Erythromycin
- Tacrolimus – non antibiotics macrolide
- Azithromycin - Unique, does not inhibit CYP3A4
- Clarithromycin
- Dirithromycin
- Roxithromycin
- Telithromycin

Aminoglycosides:

- Amikacin
- Arbekacin
- Gentamicin
- Kanamycin
- Neomycin
- Netilmicin
- Paromomycin
- Rhodostreptomycin
- Streptomycin
- Tobramycin
- Apramycin

Erythromycin was the 1st macrolide used clinically. Newer examples include clarithromycin and azithromycin. Erythromycin may **potentially interact with amiodarone, warfarin and simvastatin**

Macrolides act by inhibiting bacterial protein synthesis. If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated.

Erythromycin is used in gastroparesis as it has prokinetic properties, Promotes gastric emptying

Adverse effects of erythromycin

- GI side-effects are common
- Cholestatic jaundice: risk may be ↓ if erythromycin stearate is used
- P450 inhibitor

Quinolones are a group of antibiotics which work by inhibiting DNA synthesis and are bactericidal in nature. Examples include:

- Ciprofloxacin
- Levofloxacin

Adverse effects

- Lower seizure threshold in patients with epilepsy
- Tendon damage (including rupture) - the risk is ↑ in patients also taking steroids. Achilles tendon ruptures. Tendon damage is a well documented complication of quinolone therapy. It appears to be an idiosyncratic reaction, with the actual median duration of treatment being 8 days before problems occur

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Quinupristin & Dalfopristin Antibiotics

Overview

- Injectable streptogrammin antibiotic
- Combination of group A and group B streptogrammin
- Inhibits bacterial protein synthesis by blocking tRNA complexes binding to the ribosome

Spectrum

- Most Gram positive bacteria
- Exception: *Enterococcus faecalis*

Adverse effects

- Thrombophlebitis (give via a central line)
- Arthralgia
- P450 inhibitor

Linezolid is a type of oxazolidonone antibiotic which has been introduced in recent years. It inhibits bacterial protein synthesis by stopping formation of the 70s initiation complex and is bacteriostatic nature

Spectrum, highly active against **Gram positive** organisms including:

- MRSA (Methicillin-resistant *Staphylococcus aureus*)
- VRE (Vancomycin-resistant enterococcus)
- GISA (Glycopeptide Intermediate *Staphylococcus aureus*)

Adverse effects

- Thrombocytopenia (reversible on stopping)
- Monoamine oxidase inhibitor: avoid tyramine containing foods

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Sulfonamides: Antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS), an enzyme involved in folate synthesis.

Other uses

The sulfonamide chemical moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochlorothiazide, metolazone, and indapamide, among others), loop diuretics (including furosemide, bumetanide and torsemide) sulfonylureas (including glipizide, glyburide, among others), some COX-2 inhibitors (e. g. celecoxib) and acetazolamide.

Sulfasalazine, in addition to its use as an antibiotic, is also utilized in the treatment of inflammatory bowel disease.

Co-trimoxazole: sulfonamide antibiotic combination of trimethoprim and sulfamethoxazole, in the ratio of 1 to 5, used in the treatment of a variety of bacterial infections. The name co-trimoxazole is the British Approved Name, and has been marketed worldwide under many trade names including Septra, Bactrim, and various generic preparations. Sources differ as to whether co-trimoxazole usually is bactericidal or bacteriostatic

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Diethylcarbamazine:

There are two (**Di**) women named **Ethyl** in this **car**: **Di- ethyl-car**. You will notice that there is an elephant between Ethyl and Ethyl.

Indication:

Treatment of individual patients with certain filarial diseases. These diseases include: lymphatic filariasis caused by infection with Wuchereria bancrofti, Brugia malayi, or Brugia timori; (ELEPHANTiasis) tropical pulmonary eosinophilia, and loiasis.


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COMMONLY TESTED FACTS IN MRCP

1. Acromegaly – Diagnosis: OGTT followed by GH conc.
2. Cushings – Diagnosis:overnight dexamethasone OR 24hr urinary free cortisol. Addisons → short synacthen.
3. Rash on buttocks – Dermatitis herpetiformis (coeliac dx).
4. AF with TIA → Warfarin. Just TIA's with no AF → Aspirin
5. Herpes encephalitis → temporal lobe calicification OR temporoparietal attentuation – subacute onset i.e. Several days.
6. Obese woman, papilledema/headache → Benign Intercanial Hypertention.
7. Drug induced pneumonitis → methotrexate or amiodarone.
8. Chest discomfort and dysphagia → achalasia.
9. foreign travel, macpap rash/flu like illnes → HIV acute.
10. Bullae on hands and fragule SKIN torn by minor trauma → porphyria cutanea tarda.
11. Splenectomy → need pneumococcal vaccine AT LEAST 2 weeks pre-op and for life.
12. Primary hrperparathyroidism → high Ca, normal/low PO4, normal/high PTH (in elderly).
13. Middle aged man with KNEE arthritis → gonococcal sepsis (older people → Staph).
14. Sarcoidosis, erythema nodosum, arthropathy → Loffgrens syndrome benign, no Rx needed.
15. TREMOR postural, slow progression,titubation, relieved by OH→benign essential TREMOR AutDom. (MS – titbation, PD – no titubation)
16. Electrolytes disturbance causing confusion – low/high Na.
17. Contraindications lung Surgery → FEV dec bp 130/90, Ace inhibitors (if proteinuria analgesic induced headache.
18. 1.5 cm difference btwn kidneys → Renal artery stenosis → Magnetic resonance angiogram.
19. Temporal tenderness→ temporal arteritis → steroids > 90% ischemic neuropathy, 10% retinal art occlusion.
20. Severe retroorbital, daily headache, lacrimation → cluster headache.
21. Pemphigus – involves mouth (mucus membranes), pemphigoid – less serious NOT mucosa.
22. Diagnosis of polyuria → water deprivation test, then DDAVP.
23. Insulinoma → 24 hr supervised fasting hypoglycemia.
24. Causes of villous atrophy: coeliac (lymphocytic infiltrate), Whipples , dec Ig, lymphoma, trop sprue (Rx tetracycline).
25. Diarrhea, bronchospasm, flushing, tricuspid stenosis → gut carcinoid c liver mets.
26. Hepatitis B with general deterioration → hepaocellular carcinoma.
27. Albumin normal, total protein high → myeloma (hypercalcemia, electrophoresis).
28. HBsAg positive, HB DNA not detectable → chornic carier.
29. Inf MI, artery invlived → Right coronary artert.

30. Aut dom conditions: Achondroplasia, Ehler Danlos, FAP, FAMILIAL hyperchol,Gilberts, Huntington's, Marfans's, NFT I/II, Most porphyrias, tuberous sclerosis, vWD, PeutzJeghers.
31. X linked: Beck/Duch musc dyst, alports, Fragile X, G6PD, Hemophilia A/B.
32. Aortic Stenosis s2 paradoxical split, length proportional to severity
    Loud S1: MS, hyperdynamic, short PR. Soft S1: immobile MS, MR. Loud S2: hypertension, AS. Fixed split: ASD. Opening snap: MOBILE MS, severe near S2.
33. Mitral stenosis: loud S1 (soft s1 if severe), opening snap.. Immobile valve → no snap.
34. HOCM/MVP - inc by standing, dec by squating (inc all others). HOCM inc by valsalva, decs all others. Sudden death athlete, FH, Rx. Amiodarone, ICD.
35. MVP sudden worsening post MI. Harsh systolic murmur radites to axilla.
36. Dilated Cardiomyopathy: OH, bp, thiamine/selenium deficiency, MD, cocksackie/HIV, preg, doxorubicin, infiltration (HCT, sarcoid), tachycardia.
37. Restrictive Cardiomyopathy: sclerodermma, amyloid, sarcoid, HCT, glycogen storage, Gauchers, fibrosis, hypereosinophilia Lofflers, caracinoid, malignancy, radiotherapy, toxins.
38. Tumor compressing Respiratory tract → investigation: flow volume loop. A normal flow volume loop is often described as a 'triangle on top of a semi circle'
39. Guillan Barre syndrome: check VITAL CAPACITY.
40. Horners – sweating lost in upper face only – lesion proximal to common carotid artery.
41. Internuclear opthalmoplegia: medial longitudinal fasciculus connects CN nucleus 3-4.
42. Ipsilateral adduction palsy, contralateral nystagmus. Aide memoire (TRIES TO YANK THE ipsilateral BAD eye ACROSS THE nose). Convergence retraction nystagmus, but convergence reflex is normal. Causes: MS, SLE, Miller fisher, overdose(barb, phenytoin, TCA), Wernicke.
43. Progressive Supranuclear palsy: Steel Richardson. Absent voluntary downward gaze, normal dolls eye . i.e. Occulomotor nuclei intact, supranuclear Pathology .
44. Perinauds syndrome: dorsal midbrain syndrome, damaged midrain and superior colliculus: impaired upgaze (cf PSNP), lid retraction, convergence preserved. Causes: pineal tumor, stroke, hydrocephalus, MS.
45. Dementia, gait abnormaily, urinary incontinence. Absent papilledema→Normal pressure hydrocephalus.
46. Acute red eye → acute closed angle glaucoma >> less common (ant uveitis, scleritis, episcleritis, subconjuntival hemmorrhage).
47. Wheeles, URTICARIA , drug induced → aspirin.
48. Sweats and weight gain → insulinoma.
49. Diagnostic test for asthma → morning dip in PEFR >20%.
50. Causes of SIADH : chest/cerebral/pancreas Pathology , porphyria, malignancy, Drugs (carbamazepine, chlorpropamide, clofibrate, atipsychotics, NSAIDs, rifampicin, opiates)

51. Causes of Diabetes Insipidus: Cranial: tumor, infiltration, trauma Nephrogenic: Lithium, amphoteracin, domeclocycline, prologed hypercalcemia/hypornatremia, FAMILIAL X linked type
52. Bisphosphonates:inhibit osteoclast activity, prevent steroid incduced osteoperosis (vitamin D also).
53. Returned from airline flight, TIA→ paradoxical embolus do TOE.
54. Alcoholic, given glucose develops nystagmus → B1 deficiency (wernickes).
55. Confabulation→korsakoff.
56. Mono-artropathy with thiazide → gout (neg birefringence). NO ALLOPURINOL for acute.
57. Cause of gout → dec urinary excretion.
58. Gout – blood urate high/low/normal, joint aspirate pos birif, ppt thiazides, NO allopurinol/aspirin in acute phase
59. Painful 3rd nerve palsy → posterior communicating artery aneurysm till proven otherwise
60. Late complication of scleroderma → pulmonaryhypertention plus/minus fibrosis.
61. Causes of erythema mutliforme: lamotrigine
62. Vomiting, abdominal pain, hypothyroidism → Addisonian crisis (TFT typically abnormal in this setting DO NOT give thyroxine).
63. Mouth/genital ulcers and oligarthritis → behcets (also eye /SKIN lesions, DVT)
    mixed drug overdose most important step → Nacetylcysteine (time dependent prognosis)
64. Cavernous sinus syndrome - 3rd nerve palsy, proptosis, periorbital swelling, conj injection
65. Asymetric parkinsons → likely to be idiopathic
66. Obese, NIDDM ♀ with abnormal LFT's → NASH (non-alcoholic steatotic hepatitis)
67. Fluctuating level of conciousness in elderly plus/minus deterioration → chronic subdural. Can last even longer than 6 months
68. Sensitivity → TP/(TP plus FN) e.g. For SLE - ANA highly sens, dsDNA:highly specific RR is 8%. NNT is -→ 100/8 → 50/4 → 25/2 → 13.5
69. Ipsilateral ataxia, Horners, contralateral loss pain/temp → PICA stroke (lateral medulary syndrome of Wallenburg)
70. Renal stones (80% calcium, 10% uric acid, 5% ammonium (proteus), 3% other). Uric acid and cyteine stone are radioluscent.
71. Hyperprolactinemia (gallactorrohea, amenorrohea, low FSH/LH) → causes are: (metoclopramide, chlorpromazine, cimetidine NOT TCA's), pregnancy, PCOS, pit tumor/microadenoma, stress.
72. Distal, asymetric arthropathy → PSORIASIS
73. Episodic headache with tachycardia → Pheochromocytoma
74. Very raised WCC → ALWAYS think of leukemia.

75. Diagnosis of CLL → immunophenotyping NOT cytogenetics, NOT bone marrow

76. Prognostic factors for AML → bm karyotype (good/poor/standard) → WCC at diagnosis.

77. Pancytopenia with raised MCV → check B12/folate first (other causes possble, but do this FIRST). Often associayed with phenytoin use → ↓ folate

78. Miscariage, DVT, stroke → LUPUS anticoagulant → lifelong anticoagulation
Hb elevated, dec ESR → polycythemua (2ndry if paO2 low)

79. Anosmia, delayed puberty → Kallmans syndrome (hypogonadotrophic hypogonadism)

80. Commonest finding in G6PD hamolysis → haumoglobinuria

81. Flank pain, urinalysis:blood, protein → renal vein thrombosis. Causes: nephrotic syndrome, RCC, amyloid, acute pyelonephritis, SLE (atiphospholipid syndrome which is recurrent thrombosis, fetal loss, dec plt. Usual cause of cns manifestations assoc with LUPUS ancoagulant, anticardiolipin ab)

82. Anemia in the elderly assume GI malignancy

83. Hypothermia, acute renal failure → rhabdomyolysis (collapse assumed)

84. Burning, Pain, numbness anteriolateral thigh → meralgia paraesthesia (lat cutaneous nerve compression usally by by ing ligament)

85. Diagnosis of hemochromatosis: screen with Ferritin, confirm by tranferrin saturation, genotyping. If nondiagnostic do liver biopsy 0.3% mortality

86. 40 mg hidrocortisone divided doses (bd) → 10 mg prednisolone (ie. Prednislone is x4 stronger)

87. BTS: TB guidlines – close contacts → Heaf test → positive CXR, negative → repeat Heaf in 6 weeks. Isolation not required.

88. Diptheria → exudative pharyngitis, lymphadenopathy, cardio and neuro toxicity.

89. Indurated plaques on cheeks, scarring alopecia, hyperkeratosis over hair follicles →>Discoid LUPUS

90. Wt loss, malabsoption, inc ALP → pancreatic cancer

91. Foreign travel, tender RUQ, raised ALP → liver abscess do U/S

92. Wt loss, anemia (macro/micro), no obvious cause → coeliac (diarrhea does NOT have to be present)

93. Hematuria, proteinuria, best investigation → if glomerulonephritis suspected → renal biopsy

94. Venous ulcer treatment → exclude arteriopathy (eg ABPI), control edema, prevent infection, compression bandaging.

95. Malaria, incubation within 3/12. can be relapsing /remitting. Vivax and Ovale (West Africa) longer imcubation.

96. Fever, lymphadenopathy, lymphocytosis, pharygitis →EBV → heterophile antibodies

97. GI bleed after endovascular AAA Surgery → aortoenteric fistula

98. Young girl – suspect Anorexia Nervosa – linugo hair

99. Functional hypogonadotrophic hypogonadism → amennorhea. LH and FSH both low. All other hormones are usually normal. Ferritin low.

100. Reiters Syndrome – arthritis, uveitis, urethritis – Chlymidia, campylobacter, Yersinia, SALMONELLA , Shigella. Balanisits.

101. PKD – aut dom Chr 16/4 assoc berry aneurysm, mitral/aortic regurg

102. Diag of PKD → renal US even if think anorexia nervosa

103. Porphyria – photosensitivity, blisters, scars with millia, hypertrichosis

104. Vitiligo – commonest assoctions pernicious anemia → type 1 DM , autoimmune addisons, autoimmune thyoid dx

105. Peripheral neuropathy – a) B12 – rapid, dorsal columns (joint pos, vibration), sensory ataxia, pseudoathetosis of upperlimbs b) diabetic – slow, spinothalamic (pain, temp?) c)alcohol – slow progressive, spinothalamic d) Pb – motor upper limbs

106. CNS abnormalities in HIV: toxoplaasmosis (ring enhancing), lymphoma (solitary lesion). HIV encephalopathy, progressive multifocal leucoencephalopathy (PML – demylination in advanced HIV, low attenuation lesions)

107. Travellers diarrohea: chronic (>2 WEEKS) giardia (incidious onset rx. Metronidazole), SALMONELLA (serious systemic illness), E.coli (rx. Ciprofloxacin) , Shigella

108. Renal syndrome – minimal change disease, membanous, IgA nephropathy, post-streptococcal.

109. If you see blood on urinalysis forget about RAS

110. Thyroid Malignancy – tend to be non-functional, anaplastic has worse prognosis, local infiltration → dysphagia, vocal cord paralysis

111. Fatiguability → myasthenia gravis

112. Fasciculations → Motor neurone diease

113. Silvery white scale → PSORIASIS

114. Hypopigmented → vitiligo/pityriasis versicolor

115. Pretibial myxedema → Graves (NOT lid lag, NOT exopthalmus)

116. R. Arthritis with nephritic syndrome → looks for amyloidosis, even by rectal biopsy.

Disorder	Investigation of choice
Cushing	Overnight Dexamethasone Test
Cushing- vs. Pseudo-cushing	Insulin Stress Test
Addison	Short Synacthen Test
Pheochromocytoma	24^{H} Urinary Catecholamines
Acromegaly	Oral Glucose Tolerance Test


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